RESEARCH ON THE HYDROSULFATES OF THE ALKALI ELEMENTS

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The hydrosulfates of the alkali elements are produced when sulfuric acid acts upon their chlorides, normal sulfates, and other salts under certain conditions. The utilization of hydrosulfates for the acidic decomposition of certain ores and for the sulfating fusion of different substances in analytical chemistry and chemical technology is largely based upon their conversion at high temperature into pyrosulfates and then into normal sulfates, sulfur trioxide being given off. Far from enough work has been done on the physicochemical properties of the hydrosulfates. There is almost no information, for example, on their hydration, melting points, and limits of thermal stability.

We have prepared the pure hydrosulfates of all the alkali elements, determined the melting points of these compounds, investigated the behavior of the hydrosulfates when heated, and established the temperatures at which they begin to change into pyrosulfates.

The information on the production of lithium hydrosulfate is highly contradictory. Weber [1] and Kobbe [2] believe that lithium does not constitute a compound with the composition of $LiHSO_4$ at all. According to Schultz [3], this compound is precipitated from a solution of the normal sulfate in sulfuric acid, while Lescoeur [4] asserts that the salt is produced only when the sulfuric acid employed is a monohydrate. Dunnicliff's efforts [5] to crystallize the hydrosulfate from aqueous solutions of normal lithium sulfate that contained a large excess of sulfuric acid resulted in the formation of crystals of the monohydrate of normal lithium sulfate, more or less contaminated with sulfuric acid. The acid is eliminated entirely by the action of ether. The composition of the crystals was as follows: 38.71% sulfuric acid; 57.02% normal lithium sulfate; 4.27% water. According to Dunnicliff, the hydrosulfate ought to have 47.11% of sulfuric acid and 52.89% of the normal lithium sulfate.

The hydrosulfates of sodium and potassium were prepared by the generally used method of reacting the respective chlorides or normal sulfates with sulfuric acid.

Erdmann [6] obtained rubidium hydrosulfate as a bright, oily, slightly mobile liquid by dissolving rubidium salts with a volatile acid in sulfuric acid and evaporating in a platinum cup. When chilled, the hydrosulfate solidified into a beautiful ray-like mass. Dunnicliff [5] obtained rubidium hydrosulfate by treating the chloride or the normal sulfate with the theoretical quantity of sulfuric acid. The solution was evaporated to dryness, the residue being melted. The resulting product was pulverized in a hot agate mortar and then treated with seven times its weight of absolute alcohol and washed with ether. The percentage of sulfuric acid in the residue was found to be 29.93%. The theoretical percentage of H_2SO_4 in rubidium sulfate is stated by the author to be 26.86%. Endeavors to secure rubidium hydrosulfate by treating the nitrate with a slight excess of sulfuric acid and then evaporating the solution and heating the residue were unsuccessful, for it was extraordinarily difficult to eliminate the traces of acid even by prolonged heating. Browning [7] met with the same lack of success.

Kirchhoff and Bunsen [8] produced cesium hydrosulfate by treating the carbonate with an excess of sulfuric acid and then heating the mixture until the excess acid had been eliminated. The cooled crystalline mass was dissolved in water, the resulting hydrosulfate settling out as small crystals when the solution was slowly heated. Dunnicliff [5] secured cesium hydrosulfate by the same method he used to get the rubidium hydrosulfate.

As Berthelot [9] pointed out, sodium and potassium pyrosulfates are converted into the hydrosulfates when they are dissolved in water. We employed this method to secure pure hydrosulfates of all the alkali elements. Samples of the pyrosulfates, prepared from the normal sulfates or chlorides by heating them with sulfuric acid [10], were dissolved in a slight excess of water and allowed to stand in a desiccator over phosphoric anhydride. The hydrosulfates crystallized out within 40-60 hours, the solutions gradually crystallizing completely. The crystals were kept in the desiccator until completely dried. Their weight corresponded exactly to the conversion of the original pyrosulfates into anhydrous hydrosulfates.

TABLE 1

Composition of Hydrosulfates
Prepared by Evaporating
Pyrosulfate Solutions

Compound	% of SO_3	
	Experimental	Calculated
$LiHSO_4$.....	76.87	76.97
$NaHSO_4$....	66.58	66.68
$KHSO_4$......	58.74	58.81
$RbHSO_4$.....	43.87	43.86
$CsHSO_4$.....	34.82	34.81

TABLE 2

Melting Points of
Hydrosulfates of
the Alkali Elements

Compound	M.p.
$LiHSO_4$.....	$104+0.5°$
$NaHSO_4$....	186
$KHSO_4$.....	216
$RbHSO_4$....	285
$CsHSO_4$....	110

To check whether the hydrosulfates of the alkali elements produce hydrates with water under our experimental conditions, we re-treated the crystals with a small amount of water. The resulting solutions were set aside to crystallize in the air instead of in a desiccator over phosphoric anhydride, as in the first experiment. The crystals that settled out within 120-160 hours had their original weight. This proved that the hydrosulfates of the alkali elements we had prepared were anhydrous. The composition of the prepared hydrosulfates is given in Table 1. The analyses for SO_3 content were made by the usual gravimetric method, a weighed sample of the preparation being converted into barium sulfate.

The preparation of the anhydrous potassium hydrosulfate agrees with the observations made by Graham [11], but contradicts the researches of Montemartini [12] who believes that $KHSO_4$ crystallizes with one molecule of hydration water.

The melting points of the hydrosulfates we had prepared were determined visually by heating a small portion of the substance in a capillary, using the device employed to measure the melting points of organic substances. The thermometer, with the capillary alongside it, was placed in the empty interior vessel of the device, without any vaseline. Tests showed that the convection air currents within the interior vessel transmit the temperature of the sulfuric acid in the outer vessel more quickly, thus ensuring more accurate determinations of the melting point. The thermometer was tested in advance at the melting point of ice and the boiling point of water. The melting points of the hydrosulfates, as established by a series of measurements, are listed in Table 2.

Lithium hydrosulfate melts at 160°, according to Schultz [3], and at 120°, according to Lescoeur [4]. Kendall and Landon [13] determined the melting points of sodium and potassium hydrosulfates as 186° and 218.6° respectively. Cambi and Bozza [14] give the melting point of sodium hydrosulfate as 185.7° and 213.8°, 214°, and 218° for potassium hydrosulfate. Older determinations of the potassium hydrosulfate melting point are 200° [15] and 210° [16].

The change in melting points in the alkali hydrosulfate series is typical of salts with an easily polarizable anion. The progressive rise in the melting point as we pass from lithium hydrosulfate to the hydrosulfates of sodium, potassium, and rubidium evidently depends upon a decrease in the polarizing action of the cations as their radii increase in size. The HSO_4^{-1} anion is perceptibly polarized apparently even when acted upon by a potassium ion. As we pass from the hydrosulfate of rubidium to the cesium salt, we observe a substantial drop of the melting point. This is most likely due to a decrease in the strength of the compound's crystal lattice, as a result of the large ionic radius of cesium.

When we compare these figures with those for the pyrosulfates [10], we should bear in mind that the potassium salt has the highest melting point among the latter, whereas the maximum melting point is shifted to the rubidium salt in the hydrosulfates. It is evident that the HSO_4^{-1} ion is more greatly deformed than the $S_2O_7^{-2}$ ion.

The hydrosulfates have melting points that average some 100-200° lower than the corresponding pyrosulfates. Their crystal lattices are not very strong, apparently because the HSO_4^{-1} ion is monovalent, while the $S_2O_7^{-2}$ ion is divalent. Moreover, the hypothetical high polarizability of the HSO_4^{-1} anion may likewise be a factor here.

One of the important properties of the hydrosulfates is their transformation into pyrosulfates at rather low temperatures, water being split out. According to Baum [17], "dark-red heat" is a prerequisite for this process, but the reaction takes place even at 260-320° when the preparation is heated at reduced pressure. According to Cambi and Bozza [14], sodium hydrosulfate slowly gives off water at approximately its melting point and is transformed into the pyrosulfate.

The thermal stability of the hydrosulfates was determined by taking samples of the latter (approximately 1 g), placing them in porcelain crucibles, and heating them in a drying cabinet, with the temperature raised gradually, until their weights remained constant.

TABLE 3

Heating Hydrosulfates of the Alkali Elements

Compound	Temp.at which the conversion to the pyrosulfate sets in	Yield of $Me_2S_2O_7$ from the $MeHSO_4$ (% of theoretical)	% SO_3 in the heating residue	
			Experimental	Calculated for the pyrosulfate
$LiHSO_4$...	90-100°	100.02	84.08	84.27
$NaHSO_4$..	140-150	99.70	72.07	72.09
$KHSO_4$....	160-170	100.00	62.89	62.96
$RbHSO_4$...	170-200	98.21	46.00	46.14
$CsHSO_4$...	150-180	99.94	36.18	36.23

The temperature at which the first loss of weight of at least 0.005 g was observed was taken as that at which the decomposition of the hydrosulfates sets in. In every case, the end product was a pyrosulfate, as shown by analysis. The temperatures at which the hydrosulfates are converted into pyrosulfates, and the percentages of SO_3 found in the resulting products are listed in Table 3.

According to Van Arkel and de Boor [18], cesium hydrosulfate is the most stable of the hydrosulfates of the alkali elements. Our findings indicate that its stability does not exceed that of rubidium hydrosulfate; on the contrary, it begins to decompose at a somewhat lower temperature. Only cesium hydrosulfate melts at a temperature that is lower than the point at which the salt begins to decompose. These temperatures practically coincide in the case of lithium hydrosulfate. It should be stated, however, that the hydrosulfates decompose extremely slowly at low temperatures. Cesium hydrosulfate, for example, begins to lose weight in the 150-180° range, but it has to be heated to 350° for 3-5 hours for decomposition (of a sample of about 2 g of the salt) to be complete. Thus, melting the salt rapidly produces no perceptible decomposition.

The low stability of the hydrosulfates, compared to the normal sulfates and the pyrosulfates must be attributed to the presence of the hydrogen ion in the hydrosulfate anion. The hydrogen ion, whose effective radius is small, penetrates the electronic shell of the anion and causes strong one-sided polarization of the latter, resulting in a relative decrease in the stability of the compound.

The polarizing action of the cation linked to the anion results in the phenomenon of counterpolarization, diminishing the stability of the compound. In the case of the hydrosulfates of the alkali elements, there is no doubt that the predominant factor influencing their stability is the decrease in the polarizing effect of the alkali element cation, due to the increasing radius as we pass from lithium to rubidium. This increases the compounds' stability and raises the temperature at which decomposition sets in as we travel along the series.

The somewhat lower stability of cesium hydrosulfate than that of rubidium sulfate may be due to the substantial polarizability of the cesium ion itself. The resulting reinforcement of the bond between the cesium and the oxygen atoms in the HSO_4^{-1} anion may weaken the bond of the latter's hydrogen atom and facilitate the splitting out of water. A related thermal decomposition of certain oxyacids has been described by one of the present authors [19] in the case of rubidium and cesium wolframates.

SUMMARY

1. The hydrosulfates of all the alkali elements have been prepared by evaporating aqueous solutions of their pyrosulfates to dryness at room temperature. This yields crystalline anhydrous hydrosulfates.

2. The melting points of the resulting compounds have been determined. Rubidium hydrosulfate has the highest melting point (285°). The melting points drop as we pass to the hydrosulfates of potassium (216°), sodium (186°), and lithium (104°), though cesium hydrosulfate's melting point is likewise low (110°).

3. The temperatures at which the hydrosulfates of the alkali elements begin to be transformed into pyrosulfates have been established. Rubidium hydrosulfate is the most stable (decomposition setting in at 170-200°). The stability of the hydrosulfates diminishes as we pass to potassium, sodium, and lithium (the temperatures at which decomposition sets in being 160-170°, 140-150°, and 90-100°, respectively). Cesium hydrosulfate decomposes somewhat more readily than rubidium hydrosulfate (150-180°).

4. The behavior patterns involved in the changes of the melting point and of the thermal stability of the hydrosulfates of the alkali elements have been discussed from the standpoint of concepts of polarizing action and polarizability of ions.

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RESEARCH ON THE PYROSULFATES OF THE ALKALI ELEMENTS

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The applications of sodium and potassium pyrosulfates are of considerable importance in analytical chemistry and chemical technology. They are employed to decompose certain rare-earth and earth-acid minerals, such as euxenite, samarskite, tantalite, and the like, and to convert some oxides that are only slightly soluble in acids, such as Al_2O_3, Fe_2O_3, TiO_2, and the like, into salts.

The chemical action of these pyrosulfates is based upon the fact that they decompose, giving off sulfur trioxide, at temperatures above the boiling point of sulfuric acid and hence cause strong sulfatizing action.

Comparatively little research has been done as yet upon the pyrosulfates. There are no dependable data on their melting points and decomposition temperatures, while for some of the alkali elements there are no descriptions of the properties of their pyrosulfates.

We have prepared the pyrosulfates of all the alkali elements, measured their melting points and determined the temperatures at which they begin to be converted into the normal sulfates when calcined under various conditions (in air, in the presence of ammonium carbonate, in a current of ammonia, and in a current of hydrogen).

Flood and Ferland [1] produced lithium pyrosulfate by heating normal lithium sulfate to about 300° in an atmosphere of sulfur trioxide.

Weber [2] states that sodium and potassium pyrosulfates, of the $Me_2S_2O_7$ type, can be produced by reacting the thoroughly dried normal sulfates with sulfur trioxide in a sealed tube, heating the former to 150° and the latter to the temperature of a water bath. The same author asserts that normal rubidium and cesium sulfates react with sulfur trioxide to form the compounds $Rb_2O \cdot 8SO_3(Rb_2S_8O_{25})$ and $Cs_2O \cdot 8SO_3(Cs_2S_8O_{25})$, respectively, which readily give off 6 molecules of sulfur trioxide when heated, yielding the usual pyrosulfates.

According to Cambi and Bozza [3], sodium pyrosulfate is produced by reacting the sulfate with sulfur trioxide at 450°, the temperature required for potassium pyrosulfate being 470°.

Browning [4] states that when salts of the alkali elements and volatile acids are treated with an excess of sulfuric acid and heated to constant weight at 250-270°, they yield the hydrosulfate and pyrosulfate of lithium, pyrosulfates of the $Me_2S_2O_7$ type of sodium and potassium, and the $MeHSO_4$ hydrosulfates of rubidium and cesium.

According to Erdmann [5], rubidium pyrosulfate can be produced by dissolving a rubidium salt with a volatile acid in an excess of sulfuric acid, then evaporating the solution in a platinum cup, and heating the resulting hydrosulfate.

We have produced the pyrosulfates by reacting sulfuric acid with the normal sulfates or chlorides of the alkali elements.

Lithium pyrosulfate was produced by treating the normal sulfate with the calculated quantity of dilute sulfuric acid. The mixture was evaporated on a water bath to drive off the excess water and then heated to 220° until the reaction was complete. The pyrosulfates of sodium and potassium were prepared by treating the normal sulfates with concentrated sulfuric acid and then heating the mixtures until the reactions were complete, the temperature required being 270° for sodium and 370° for potassium.

TABLE 1

Analysis of Preparations of Pyrosulfates of the Alkali Elements

Compound	% SO_3	
	Experimental	Calculated
$Li_2S_2O_7$	84.16	84.27
$Na_2S_2O_7$	71.98	72.09
$K_2S_2O_7$	62.90	62.96
$Rb_2S_2O_7$	46.14	46.14
$Cs_2S_2O_7$	36.24	36.23

Rubidium pyrosulfate was prepared by heating a mixture of the chloride with a 20% excess of sulfuric acid, the temperature being gradually raised to 400°, until the weight remained constant.

TABLE 2

Melting Points of Pyrosulfates of the Alkali Elements

Compound	M.p.
$Li_2S_2O_7$.....	$205\pm2°$
$Na_2S_2O_7$....	402
$K_2S_2O_7$.....	440
$Rb_2S_2O_7$....	401
$Cs_2S_2O_7$....	280

Cesium pyrosulfate was produced by treating the normal sulfate or chloride with concentrated sulfuric acid. When the sulfate was used, the reaction mass was heated for 6.5 hours, the temperature being gradually raised to 500°, until the weight remained constant; with the chloride, heating lasted 18 hours, with the temperature raised to 370°.

The resulting preparations were analyzed in the usual manner, the SO_3 content being determined as $BaSO_4$. The results are listed in Table 1.

There are only a few figures given in the literature for the melting points of the pyrosulfates. Cambi and Bozza [3] found the melting point of sodium pyrosulfate to be 400.9°. Schultz-Sellack [6] states that potassium pyrosulfate melts far above 300°. We determined the melting points of our preparations by means of a platinum—platinum-rhodium thermocouple, from the cooling curves. The results of our measurements are given in Table 2.

The melting points are progressively higher in the series of lithium, sodium, and potassium salts. The potassium pyrosulfate has the highest melting point of all the compounds tested. The melting points drop off appreciably as we pass on to the rubidium and cesium salts. The general pattern of changes in the melting points of the pyrosulfates recalls the analogous picture in the iodides of the alkali elements. Here again, the readily polarizable $S_2O_7^{-2}$ anion is polarized by the sodium ion and more strongly so by the lithium ion, thus lowering the melting point as the ionic radius of the cation is diminished. This sort of polarizing action no longer exists, obviously, in the pyrosulfates of potassium, rubidium, and cesium. The successive drop of the melting points in this series of compounds must be due to the decrease in the stability of their crystal lattices as the ionic radii of the cations increase.

TABLE 3

Hygroscopicity of Pyrosulfates of the Alkali Elements

Compound	Time in air, hours	Mean hourly gain in weight, %
$Li_2S_2O_7$...	150	0.51
$Na_2S_2O_7$...	140	0.15
$K_2S_2O_7$...	140	0.02
$Rb_2S_2O_7$...	24	None
$Cs_2S_2O_7$...	115	0.007

We have found the pyrosulfates of the alkali elements to be more or less hygroscopic, with the sole exception of rubidium pyrosulfate. After these compounds had been exposed to the air for a long time, they exhibited the gains in weight set forth in Table 3.

The hygroscopicity of the pyrosulfates diminishes progressively from lithium to potassium; it is not present in rubidium, but reappears slightly in cesium. It is probable that this change in hygroscopicity is not fortuitous, but reflects the feasibility of adding water and of the ensuing hydrolysis of the compounds, depending upon the ionic radius of the alkali element and, he hence, the strength of the base formed by the given salt. The slight hygroscopicity of the cesium pyrosulfate may be due to the innate polarizability of the cesium ion when acted upon by the dipole of the water molecule that penetrates into the crystal lattice of the pyrosulfate.

The pyrosulfates' hygroscopicity must be allowed for whenever they are utilized.

We possess the following information on the temperatures at which the pyrosulfates are converted into normal sulfates. Cambi and Bozza [3] state that sodium pyrosulfate is converted into the normal sulfate at "red heat." At "red heat" rubidium pyrosulfate merely gives off some sulfur trioxide, being fully converted into the normal sulfate when the temperature is raised still further.

TABLE 4

Temperatures at Which the Pyrosulfates of the Alkali Elements Begin to Change into the Normal Sulfates when Heated in Air

Compound	Temp. at which the pyrosulfate begins to change into the normal sulfate
$Li_2S_2O_7$....	200-220°
$Na_2S_2O_7$...	320-370
$K_2S_2O_7$....	370-420
$Rb_2S_2O_7$...	400-450
$Cs_2S_2O_7$....	500-520

Flood and Ferland [1] investigated the thermal dissociation of some pyrosulfates in an atmosphere of sulfur trioxide at pressures of 1 to 0.4 atm. These authors found that the stability of the pyrosulfates rose progressively in the following series Ag—Li—Na and Tl—K. The systems of the normal sulfate and the pyrosulfate were investigated in various temperature ranges:

$$Li_2SO_4-Li_2S_2O_7 \quad 371-427°$$
$$Na_2SO_4-Na_2S_2O_7 \quad 555-655°$$
$$K_2SO_4-K_2S_2O_7 \quad 653-727°$$

We have investigated the temperatures at which the transition of the pyrosulfates to normal sulfates sets in when they are heated in air. Samples of the preparation, weighing 0.8-1 g approximately, were heated in porcelain

crucibles in an electric furnace to constant weight, the temperature being gradually raised and the weight being checked at intervals. The temperature at which the first loss of weight amounting to at least 0.005 g was taken to be the temperature at which the pyrosulfate begins to decompose.

The SO_3 content of the end products corresponded to that in the normal sulfates.

The temperatures at which we found the pyrosulfates beginning to change into the normal sulfates are listed in Table 4.

It should be noted that sulfur trioxide begins to split out of the pyrosulfates of sodium and potassium at temperatures that are about 50° below their melting points. This process is a time-governed one, however, a rather long heating period being required for complete decomposition. Thus, melting the salt rapidly does not entail any perceptible decomposition.

The pyrosulfates of lithium and rubidium break down immediately after these compounds are fused. Cesium pyrosulfate begins to decompose far above its melting point.

The rate at which the pyrosulfates are converted into the normal sulfates is indicated by the fact that in cesium pyrosulfate, for example, the decomposition reaction sets in slowly at 500-520°, becomes more intensive at 550-570°, and is completed only at 600°. The complete transformation of the sample used (0.8 g) into the normal sulfate required heating for a total of 18 hours.

When we compare the temperatures at which the various pyrosulfates begin to change into the normal sulfates, we find that the thermal stability of the pyrosulfates of the alkali elements increases progressively from lithium to cesium. Apparently, as the ionic radius of the cation increases in size, the polarizing effect of the latter, which is located in the outer sphere of the coordination compound:

$$\begin{bmatrix} O \\ OSO \\ SO_4 \end{bmatrix} Me_2$$
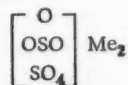
upon the anion progressively diminishes resulting in an increase in the stability of the pyrosulfates. This pattern of behavior conforms to the well-known general rules governing the manner in which the stability of coordination compounds depends upon the properties of the cation in the second sphere of these compounds [7].

The fact that the thermal stability of the pyrosulfate is less than that of the normal sulfates [8] may be attributed to the presence of an appreciable counterpolarization effect in the anion due to the presence of a second sulfur ion. As has been stated above, rubidium and cesium compounds of the $Me_2O \cdot 8SO_3 (Me_2S_8O_{25})$ type, i.e., containing even more sulfur atoms in the anion, are extremely unstable, being readily converted into the ordinary pyrosulfates when heated.

As indicated in the literature, the transformation of pyrosulfates into the normal sulfates by the application of heat is facilitated by the addition of ammonium carbonate. In the analytical determination of potassium as its normal sulfate, for example, ammonium carbonate is employed to decompose the $K_2S_2O_7$ mixed with the K_2SO_4 — "if solid ammonium carbonate is added, the SO_3 is converted into ammonium sulfate, which is highly volatile and can be eliminated at a lower temperature without any loss of potassium" [9]. We ran experiments on the effect of ammonium carbonate upon the stability of the pyrosulfates of all the alkali elements to check the correctness of these instructions.

As is seen from the figures in Table 5, we found that when the pyrosulfates of the alkali elements, with the sole exception of rubidium pyrosulfate, are heated with ammonium carbonate, they actually do change into the normal sulfates at lower temperatures. The effect is not too great, however. The addition of ammonium carbonate produces a drop of 30-50° in the temperature at which the pyrosulfates begin to decompose, the drop attaining 100° only in the case of cesium pyrosulfate.

References in the literature also state that the conversion of hydrosulfates, and hence of the pyrosulfates, of the alkali elements into the normal sulfates is accelerated in a current of ammonia. Hinrichsen and Sachsel [10], for example, recommend that rubidium pyrosulfate be calcined in a current of NH_3 to prepare the normal sulfate.

A sample of the pyrosulfate was placed in a porcelain boat and brought to constant weight at 700-750° in a current of ammonia, then placed within another protective boat and inserted into the porcelain tube of an electric furnace whose temperature was gradually raised. When the required temperature was attained, a current of dry ammonia was passed through the tube at the rate of 6 liters per hour.

TABLE 5

Effect of Adding Ammonium Carbonate Upon the Temperature at Which Pyrosulfates Begin to Change into Normal Sulfates

Compound	Temperatures at which pyrosulfates begin to change into normal sulfates	
	With $(NH_4)_2CO_3$	Without $(NH_4)_2CO_3$
$Li_2S_2O_7$.....	170-220°	200-220°
$Na_2S_2O_7$....	270-320	320-370
$K_2S_2O_7$.....	320-370	370-420
$Rb_2S_2O_7$....	400-450	400-450
$Cs_2S_2O_7$....	400-420	500-520

After heating was over, the pyrosulfate was cooled in a current of air that had been previously dried in wash bottles containing sulfuric acid and in towers filled with phosphoric anhydride.

Our first experiments on heating lithium pyrosulfate in a current of ammonia showed that its conversion into the normal sulfate was a complicated process. At first, its weight increases due to the addition of ammonia to the pyrosulfate and the formation of an intermediate compound, which is transformed into the normal sulfate as the temperature continues to rise.

We found that ammonia is added even at room temperature (20-25°), the time required for this process being proportional to the amount of pyrosulfate.

Heating the intermediate product in a current of ammonia for an hour at 120, 170, and 220° showed that the product is thermally stable in this interval as well. The behavior of the product was investigated in a current of dry air at the same temperatures. No changes were observed.

TABLE 6

% of NH_3 in the Product of the Reaction of Lithium Pyrosulfate with Gaseous Ammonia

Weight of sample,g	Ammonia found	
	g	%
0.0820	0.0067	8.17
0.0758	0.0062	8.18
0.0750	0.0062	8.27
	Average	8.21

Our hygroscopicity investigations yielded positive results. The product absorbs hygroscopic moisture, which is then given off in the current of dry air even at room temperature.

These latter observations compelled us to suppose that the substance produced by the action of gaseous ammonia upon lithium pyrosulfate was a definite chemical compound rather than a product of the adsorption of ammonia on the lithium pyrosulfate. The percentage of ammonia was determined in three samples of the preparation in order to establish the composition of this compound.

The results are given in Table 6.

The compound $Li_2S_2O_7 \cdot NH_3$ has 8.21% of ammonia. When the temperature is raised above 220°, the $Li_2S_2O_7 \cdot NH_3$ begins to give up its ammonia and then its SO_3, being transformed into the normal sulfate.

TABLE 7

Comparison of the Temperatures at Which the Pyrosulfates of the Alkali Elements are Converted into the Normal Sulfates when Heated in Currents of Ammonia and of Air

Compound	Temperatures at which pyrosulfates begin to change into normal sulfates	
	In a current of ammonia	In air
$Li_2S_2O_7$...	220-270°	200-220°
$Na_2S_2O_7$...	320-370	320-370
$K_2S_2O_7$...	370-420	370-420
$Rb_2S_2O_7$...	Converted to a sulfide	400-450
$Cs_2S_2O_7$...	370-420	500-520

Our efforts to secure analogous ammonia addition products of the pyrosulfates of the other alkali elements at room temperature or after heating all met with failure. When heated, the pyrosulfates of sodium, potassium, and cesium were converted into the normal sulfates, while the rubidium pyrosulfate was converted into the sulfide.

The temperatures at which the pyrosulfates begin to change into normal sulfates when heated in a current of ammonia are listed in Table 7.

We see from Table 7 that heating in ammonia has no perceptible effect upon the temperature at which the pyrosulfates of sodium and potassium are converted into the normal sulfates, compared to their heating in air.

Only in the case of the cesium pyrosulfate did we find the conversion temperature lowered by 100-150°. The higher temperature at which lithium pyrosulfate is converted into the normal sulfate, as compared with its heating in air, does not apply to the $Li_2S_2O_7$, but rather to its ammonia compound, $Li_2S_2O_7 \cdot NH_3$.

The singular behavior of rubidium pyrosulfate is worthy of note, it being reduced by the ammonia to the sulfide, beginning at 300-350°. At 700° the reduction product is completely volatilized.

We also ran experiments to ascertain the behavior of the pyrosulfates of the alkali elements when heated in a current of hydrogen.

TABLE 8

Comparison of the Temperatures at Which the Pyrosulfates of Alkali Elements are Converted into Normal Sulfates when Heated in Currents of Hydrogen and of Ammonia

Compound	Temperatures at which pyrosulfates are converted into normal sulfates	
	In a current of hydrogen	In a current of ammonia
$Li_2S_2O_7$...	170-220°	220-270°
$Na_2S_2O_7$...	270-320	320-370
$K_2S_2O_7$....	370-420	370-420
$Rb_2S_2O_7$...	Converted to a sulfide	Converted to a sulfide
$Cs_2S_2O_7$...	470-520	370-420

As we see from Table 8, heating in a current of hydrogen lowers the temperature at which lithium and sodium pyrosulfates are converted into their normal sulfates, compared with heating in a current of ammonia. The temperature at which the potassium pyrosulfate was converted proved to be the same in both cases, whereas the cesium pyrosulfate was converted into the normal sulfate at a higher temperature. As in the current of ammonia, the rubidium pyrosulfate yielded a sulfide.

In conclusion, we should like to state that none of the various methods of accelerating the decomposition of the pyrosulfates utilized by us yielded substantial results. The principal factor determining the rate at which a pyrosulfate is converted into a normal sulfate is the temperature. The temperatures at which the decomposition reactions of the pyrosulfates set in fix the limits within which these compounds can be heated without losing sulfur trioxide. Utilizing temperatures that are 150-200° higher makes it possible to effect rapid decomposition of the pyrosulfates.

SUMMARY

1. The pyrosulfates of all the alkali elements have been produced, their melting points measured, and the temperatures at which they begin to change into normal sulfates determined under various conditions.

2. The melting points of the pyrosulfates rise progressively from lithium (205°) through sodium (402°) to potassium (440°), after which they drop off to rubidium (401.5°) and cesium (280°).

3. The thermal stability of the pyrosulfates rises progressively from lithium to cesium. The temperature at which $Li_2S_2O_7$ begins to decompose is 200-220°, and $Cs_2S_2O_7$ is 500-520°. The pattern of changes in stability of the pyrosulfates is discussed from the standpoint of concepts of the polarizing action of ions.

4. Adding ammonium carbonate merely lowers the decomposition temperature of the pyrosulfates negligibly. This additive has no effect upon rubidium pyrosulfate.

5. Heating cesium pyrosulfate in a current of ammonia accelerates its decomposition noticeably. Under these conditions the pyrosulfate of rubidium is converted into its sulfide. The temperatures at which decomposition sets in are not affected by ammonia in the other pyrosulfates.

6. Heating rubidium pyrosulfate in a current of hydrogen results in formation of a sulfide. Heating in a current of hydrogen has no substantial effect upon the temperature at which the pyrosulfates of the other alkali elements begin to decompose.

7. It has been found that lithium pyrosulfate forms the addition product $Li_2S_2O_7 \cdot NH_3$, in a current of ammonia. The thermal stability of this compound has been investigated.

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THE ACTION OF LITHIUM HALIDES UPON ESTERS OF PHOSPHOROUS ACID

V. S. Abramov and O. D. Samoilova

There are no researches on the action of halides of the alkali elements upon esters of phosphorous acid.

We have previously [1] investigated the action of the halides of the alkali elements sodium, potassium, and lithium upon the esters of alkoxymethylphosphinic acids, finding that heat caused the metal to replace one of the ester radicals, which was evolved as an alkyl halide. The overall equation may be written as follows:

$$(RO)_2P\underset{O}{\overset{CH_2OR'}{\diagup}} + MeHal \longrightarrow \underset{O\quad OMe}{\overset{RO\quad CH_2OR'}{P}} + RHal.$$
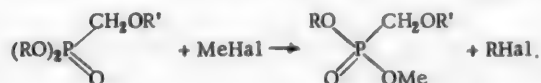
By way of analogy with these reactions we made a study of the action of the lithium halides upon esters of phosphorous acid. We found that lithium halides do not react with phosphorous acid esters at ordinary temperature, though dissolution is violent when the mixture is heated. We succeeded in distilling an alkyl halide from the reaction products, the residue consisting of a lithium salt that proved to be a lithium dialkylphosphite upon analysis. The overall reaction may be written as:

$$(RO)_3P + LiBr \longrightarrow (RO)_2POLi + RBr.$$

We reacted lithium bromide and chloride with the ethyl and butyl esters of phosphorous acid, obtaining lithium diethyl- and dibutylphosphite. Sodium iodide also acts upon esters of phosphorous acid, as has been demonstrated in preliminary tests.

The mechanism involved in these reactions must evidently be conceived of in this way: in the first stage the lithium halide is probably added to the phosphorus acid ester. This is borne out by analysis of the product secured by dissolving lithium bromide in triethylphosphite in a benzene medium, which contains 3% less phosphorus than lithium diethylphosphite, but much more than the addition product. The alkyl halide has split out during the ensuing stage.

EXPERIMENTAL

<u>Action of lithium bromide upon the butyl ester of phosphorous acid</u>. 1.74 g of lithium bromide was heated with 5 g of the butyl ester of phosphorous acid. The lithium bromide dissolved in the ester at 120°, with violent frothing. The heating lasted 30 minutes. Then butyl bromide (b.p. 98°; n_D^{20} 1.4312) was distilled from the reaction flask, the residue in the flask solidifying to a porous white mass. The salt was washed with absolute alcohol and dried in vacuum. The salt was a white powder that was insoluble in alcohol or ether, though soluble in water. The melting point of the salt was 456–460°, determined in a device using air heating.

Found %: P 15.58, 15.62. $C_8H_{18}O_3PLi$. Calculated %: P 15.50.

<u>Action of lithium chloride upon the butyl ester of phosphoric acid</u>. 0.68 gram of lithium chloride was heated in a flask with 4 g of the butyl ester of phosphorous acid. The lithium chloride dissolved in the ester at 120° with frothing. The distilled butyl chloride (b.p. 77°, n_D^{20} 1.4034) totaled 1.1 g or 74% of the theoretical. The residue was a white powder whose properties were the same as those described in the preceding experiment. M. p. 455–458°. The mixed melting point was 456–460°.

<u>Action of lithium bromide upon the ethyl ester of phosphorous acid</u>. 2.1 grams of lithium bromide was heated in a flask with 4 g of the ethyl ester of phosphorous acid in 20 ml of benzene. The lithium bromide dissolved after the mixture had been boiled for a long time. A white precipitate settled out when the mixture cooled. The benzene was decanted, and the residue was dried in vacuo on a water bath at 30–35°. The residue was a white powder that was insoluble in cold benzene, alcohol, or ether and soluble in water. The

precipitate contained halogen.

Found %: P 18.17, 18.67. $C_6H_{15}O_3PLiBr$. Calculated %: P 12.25.

Then the residue was heated in vacuo to 100°. A Beilstein test of the residue was negative.

Found %: P 21.09, 21.20. $C_4H_{10}O_3PLi$. Calculated %: P 21.52.

Action of lithium chloride upon the ethyl ester of phosphorous acid. 1.02 grams of lithium chloride were heated to 200-210° for three hours in a sealed tube with 4 g of the ethyl ester of phosphorous acid. After the tube had been cooled, it contained a white precipitate, which was washed with ether. It is soluble in alcohol and ether.

Found %: P 21.02, 21.78. $C_4H_{10}O_3PLi$. Calculated %: P 21.52.

SUMMARY

It has been found that lithium chloride and bromide react with the esters of phosphorous acid, splitting out alkyl bromide and producing a lithium dialkylphosphite.

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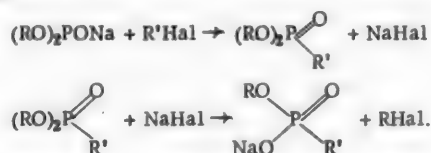
THE ACTION OF HALIDES OF THE ALKALI METALS UPON THE ESTERS OF ALKYLPHOSPHINIC ACIDS
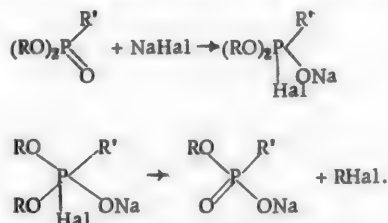
V. S. Abramov and O. D. Samoilova

The action of alkyl halides upon acid salts is one of the methods of producing esters. In this reaction a halide is produced together with the ester. It is generally believed that this reaction proceeds to completion and cannot be reversed.

In some of our preceding papers [1] we have shown that sodium halides react with esters of alkylphosphinic acids to yield a mixed salt-ester of the alkylphosphinic acid and the alkyl halide. In this case we found a reverse reaction rather than in the formation of the esters. The action of sodium halides upon esters of alkylphosphinic acids was observed in our study of the reactions of alkyl halides with salts of dialkylphosphorous acids, which proceeded as follows:

$$(RO)_2PONa + R'Hal \rightarrow (RO)_2P\overset{O}{\underset{R'}{<}} + NaHal$$

$$(RO)_2P\overset{O}{\underset{R'}{<}} + NaHal \rightarrow \overset{RO}{\underset{NaO}{>}}P\overset{O}{\underset{R'}{<}} + RHal.$$

The sodium halide produced during the first stage of the reaction is not separated from the reaction products, the reaction mass being heated. This course of the reaction cannot be regarded as a universal one, however. Only those esters of alkoxymethylphosphinic acids or, generally speaking, esters of alkylphosphinic acids, the alkyl of which contains a polar group, react with sodium halides to yield mixed salt-esters. The nature of the alkyl group likewise affects the course of this reaction. It has not been possible as yet to establish any definite pattern of behavior in these reactions, however, owing to the lack of sufficient experimental data.

A mechanism had been proposed by V. S. Abramov and E. A. Miletskova [2] for the course taken by these reactions: the sodium halide being added at the $P=O$ bond and then the alkyl halide split off:

$$(RO)_2P\overset{R'}{\underset{O}{<}} + NaHal \rightarrow (RO)_2P\overset{R'}{\underset{Hal}{<}}ONa$$

$$\overset{RO}{\underset{RO}{>}}P\overset{R'}{\underset{Hal}{\underset{ONa}{<}}} \rightarrow \overset{RO}{\underset{O}{>}}P\overset{R'}{\underset{ONa}{<}} + RHal.$$
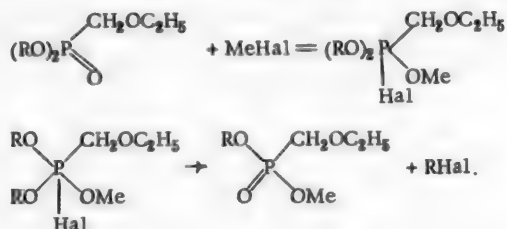
Up to the present reactions of this sort have been observed only in the action of an alkyl halide upon a sodium dialkylphosphite, with subsequent distillation of the reaction products from the reaction mixture. The sodium halide formed when the reaction is carried out in anhydrous ether is highly disperse or, more accurately speaking, is colloidal in its nature, reacting with the pure esters of the alkylphosphinic acids when it is recovered from the reaction.

The present paper sets forth the results of reacting halides of the alkali metals with esters of alkylphosphinic acids. The objective of the research was determination of how the formation of mixed salt-esters of alkylphosphinic acids was affected by the nature of the metal and the halogen.
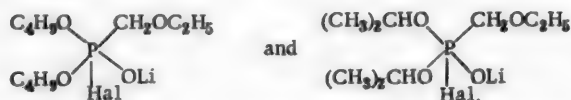
In our study of the action of halides upon esters of alkylphosphinic acids we prepared the butyl ester of ethoxymethylphosphinic acid, the butyl ester of ethyl phosphonacetate, and the isopropyl ester of ethoxymethyl-

phosphinic acid. These esters were prepared by reacting bromomethyl ethyl ether with the butyl and isopropyl esters of phosphorous acid, respectively, and reacting ethyl bromoacetate with butyl ester of phosphorous acid.
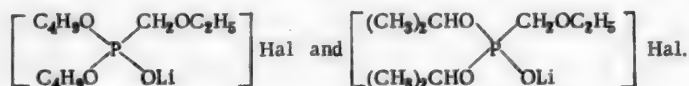
We investigated the action of sodium, potassium, and lithium chlorides, bromides, and iodides upon these esters of the alkylphosphinic acids. We found that the ordinary crystalline halides of the alkali metals react with esters of alkylphosphinic acid, yielding mixed salt-esters as follows:

$$(RO)_2P\underset{O}{\overset{CH_2OC_2H_5}{<}} + MeHal = (RO)_2P\underset{\underset{Hal}{OMe}}{\overset{CH_2OC_2H_5}{<}}$$

$$\underset{RO}{\overset{RO}{>}}P\underset{\underset{Hal}{OMe}}{\overset{CH_2OC_2H_5}{<}} \rightarrow \underset{O}{\overset{RO}{>}}P\underset{OMe}{\overset{CH_2OC_2H_5}{<}} + RHal.$$

This pattern of the action of the halides is founded solely upon the properties of the reagents and of the end products. We have not secured a direct proof that the reaction actually follows this course. Isolation of the intermediate product of the addition of the halide to the ester of the alkylphosphinic acid would constitute direct proof of the reaction mechanism. In this respect, the action of lithium halides upon the butyl and isopropyl esters of ethoxymethylphosphinic acid are of the greatest interest, because these reactions yield addition products whose composition is:

$$\underset{C_4H_9O}{\overset{C_4H_9O}{>}}P\underset{\underset{Hal}{OLi}}{\overset{CH_2OC_2H_5}{<}} \quad \text{and} \quad \underset{(CH_3)_2CHO}{\overset{(CH_3)_2CHO}{>}}P\underset{\underset{Hal,}{OLi}}{\overset{CH_2OC_2H_5}{<}}$$

where Hal = chlorine, bromine, and iodine. The structure of the resultant products may also be represented as that of phosphonium salts:

$$\left[\underset{C_4H_9O}{\overset{C_4H_9O}{>}}P\underset{OLi}{\overset{CH_2OC_2H_5}{<}}\right] Hal \quad \text{and} \quad \left[\underset{(CH_3)_2CHO}{\overset{(CH_3)_2CHO}{>}}P\underset{OLi}{\overset{CH_2OC_2H_5}{<}}\right] Hal.$$
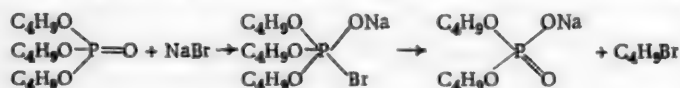
which requires further study and proof, however.

When the addition products are heated, the alkyl halide splits out, and the products are converted into the following mixed salt-esters of ethoxymethylphosphinic acid:

$$\underset{O}{\overset{C_4H_9O}{>}}P\underset{OLi}{\overset{CH_2OC_2H_5}{<}} \quad \text{and} \quad \underset{O}{\overset{(CH_3)_2CHO}{>}}P\underset{OLi}{\overset{CH_2OC_2H_5}{<}}$$

This suggested (and confirmed) mechanism for the action of halides of the alkali metals upon the esters of alkylphosphinic acids, involving the addition of the halide at the $P=O$ phosphoric bond, raised the question of the action of halides upon esters that contain a $P=O$ bond. Preliminary tests have indicated that butyl phosphate reacts with sodium bromide and iodide, yielding mixed salt-esters of phosphoric acid as follows:

$$\underset{C_4H_9O}{\overset{C_4H_9O}{\underset{C_4H_9O}{>}}}P=O + NaBr \rightarrow \underset{C_4H_9O}{\overset{C_4H_9O}{>}}P\underset{\underset{Br}{ONa}}{} \rightarrow \underset{C_4H_9O}{\overset{C_4H_9O}{>}}P\underset{O}{\overset{ONa}{<}} + C_4H_9Br$$

EXPERIMENTAL

Synthesis of the butyl ester of ethyl phosphonacetate.   28.5 grams of butyl phosphite was placed in a flask fitted with a reflux condenser, and 19 g of ethyl bromoacetate was added. After all the ester had been added, the reaction products were refluxed for one hour at 60° and then fractionated at ordinary pressure. At 100° 9 g (60% of the theoretical) of butyl bromide with n_D^{20} 1.4375 (1.4398 in the literature) was distilled off, the residue yielding (after two consecutive fractionations in vacuo) the butyl ester of ethyl phosphonacetate, with a b.p. of 182-182.5° at 16 mm. The ester yield was 1 g, or 65% of the theoretical.

n_D^{20} 1.4340; d_4^{20} 1.043; MR_D 69.65; calculated 69.27.

0.2260 g, 0.2032 g substance: 49.3, 45.4 ml NaOH (T = 0.01779). Found %: P 10.74, 11.02. $C_{12}H_{15}O_5P$. Calculated %: P 11.05.

Synthesis of the butyl ester of ethoxymethylphosphinic acid. 25 grams of monobromomethyl ethyl ether was added to 45 g of butyl phosphite, heat being evolved as addition took place. The reaction was completed by heating the reaction mixture to 150-160° for 1.5 hours. The reaction products were then fractionated. 18 grams (or 73% of the theoretical) of butyl bromide (n_D^{20} 1.4370), was driven off at 100° and atmospheric pressure. Two successive fractionations of the residue yielded the butyl ester of ethoxymethylphosphinic acid, with a b.p. of 143-143.5° at 10 mm. The ester yield was 35 g, or 77% of the theoretical.

n_D^{20} 1.4380; d_4^{20} 0.998; MR_D 64.67; calculated 64.81.

0.2160 g, 0.2556 g substance: 53.88 ml, 65.5 ml NaOH (T = 0.01779). Found %: P 12.28, 12.61. $C_{11}H_{23}O_4P$. Calculated %: P 12.3.

Synthesis of the isopropyl ester of ethoxymethylphosphinic acid. The isopropyl ester of ethoxymethylphosphinic acid was synthesized, like the butyl ester, from 35 g of isopropyl phosphite and 23 g of monobromo methyl ethyl ether. We secured 11.5 g, or 55% of the theoretical, of isopropyl bromide, with a b.p. of 59-60°. The yield of the isopropyl ester of ethoxymethylphosphinic acid, with a b.p. of 107.5-108° at 8 mm, was 23 g or 60% of the theoretical.

n_D^{20} 1.4195; d_4^{20} 1.007; MR_D 56.24; calculated: 55.44.

0.2600 g, 0.1427 g substance: 64.0 ml, 36.1 ml NaOH (T = 0.02094). Found %: P 13.55, 14.0. $C_9H_{21}O_4P$. Calculated %: P 13.80.

Action of the halides of the alkali metals on the synthesized esters of phosphinic acids. The reaction was carried out in a two-necked flask so designed that one mouth was stoppered by a hollow, ground-glass stopper containing a capillary, while the other was stoppered with a reflux condenser, which we could convert into a straight condenser by turning it upside down. This setup enabled us to drive off the liquid products after the reaction was complete without taking the apparatus apart.

An equimolecular quantity of the alkali metal halide was added to the ester of phosphinic acid. The reaction products were then refluxed until the salt dissolved. Then the straight condenser was employed to drive off the alkyl halide, which was identified by its boiling point and refractive index. What was left as a residue was a mixed salt-ester of the alkylphosphinic acid, which was washed with alcohol or recrystallized from alcohol and analyzed for its phosphorous content. It was very hard to purify the salt-ester, however, so that the phosphorus percentage found was sometimes very far from the theoretical percentage.

The results of the reaction of the alkali metal halides with the butyl ester of ethyl phosphonacetate are listed in Table 1.

The results of the reaction of sodium and potassium halides with the butyl ester of ethoxymethylphosphinic acid are summarized in Table 2.

Action of lithium chloride upon the dibutyl ester of ethoxymethylphosphinic acid. When 0.33 g of lithium chloride was heated to 105° with 2 g of the butyl ester of ethoxymethylphosphinic acid, the lithium chloride dissolved and the reagents reacted together. Part of the lithium chloride did not enter into the reaction. The compound that was produced did not dissolve in organic solvents and therefore was not purified.

Analysis of the crude product for phosphorus gave the following results:

Found %: P 6.9, 7.0, 6.72. $C_7H_{16}O_4PLi$. Calculated %: P 15.35. $C_{11}H_{25}O_4P$. Calculated %: P 10.72.

We evidently secured an addition product that contained part of the unreacted lithium chloride. The unreacted ester of the phosphinic acid was eliminated by washing the product with alcohol.

Action of lithium bromide upon the dibutyl ester of ethoxymethylphosphinic acid. When 0.69 g of lithium bromide was heated to 60-75° with 2 g of the butyl ester of ethoxymethylphosphinic acid, dissolution was complete and the lithium bromide reacted with the ester. The product crystallized when it was chilled with snow. The melting point of the crystals was 92-94°.

TABLE 1

No.	Halide	Ester of Phosphinic acid	Heating temperature	Product obtained	Calculated	Experimental	Remarks
					Analysis for P, %		
1	NaCl	$(C_4H_9O)_2P(=O)CH_2COOC_2H_5$	210-230°	Does not react	—	—	
2	NaBr	$(C_4H_9O)_2P(=O)CH_2COOC_2H_5$	190-200	$C_4H_9O\,P(=O)(ONa)CH_2COOC_2H_5$	12.6	12.78, 12.76	The salt dissolved in alcohol, precipitating the ester
3	NaI	$(C_4H_9O)_2P(=O)CH_2COOC_2H_5$	210-220	$C_4H_9O\,P(=O)(ONa)CH_2COOC_2H_5$	12.6	12.08, 12.45	

TABLE 2

No.	Halide	Ester of Phosphinic acid	Heating temperature	Product obtained	Analysis for P,%		Distillation temperature	Isolated alkyl halide	
					Calc.	Experi.		Boiling pt.	n_D^{20}
1	NaCl	$(C_4H_9O)_2P(=O)CH_2OC_2H_5$	210-220°	Does not react	—	—	—	—	—
2	NaBr	$(C_4H_9O)_2P(=O)CH_2OC_2H_5$	200-210	$C_4H_9O\,P(=O)(ONa)CH_2OC_2H_5$	14.20	14.22, 13.97	220-230°	100°	1.4368
3	NaI	$(C_4H_9O)_2P(=O)CH_2OC_2H_5$	210-217	$C_4H_9O\,P(=O)(ONa)CH_2OC_2H_5$	14.20	14.30, 13.98	220-230	128	1.4795
4	KBr	$(C_4H_9O)_2P(=O)CH_2OC_2H_5$	150-160	$C_4H_9O\,P(=O)(OK)CH_2OC_2H_5$	13.22	13.55, 13.10	200-210	100	1.4305
5	KI	$(C_4H_5O)_2P(=O)CH_2OC_2H_5$	150-160	$C_4H_9O\,P(=O)(OK)CH_2OC_2H_5$	13.22	12.70, 13.00	200-215	128	1.4795

TABLE 3

No.	Halide	Ester of Phosphinic acid	Heating temperature	Product obtained	Analysis for P,%		Distillation temperature	Isolated alkyl halide	
					Calc.	Experi.		Boiling pt.	n_D^{20}
1	NaCl	$(C_3H_7O)_2P(=O)CH_2OC_2H$	250°	Does not react	—	—	—	—	—
2	NaBr	$(C_3H_7O)_2P(=O)CH_2OC_2H_5$	180 - 190°	$C_3H_7O\,P(=O)(ONa)CH_2OC_2H_5$	15.5	14.6, 14.9	200-210	57-58°	1.4202

0.1043 g, 0.1800 g substance: 16.4 ml, 26.9 ml NaOH (T = 0.02094). 0.1020 g substance: 0.0527 g AgBr. Found %: P 8.70, 8.25; Br 23.0. $C_{11}H_{25}O_4$ BrPLi. Calculated %: P 9.14; Br 23.55.

The addition product was heated to 150-160° in a flask attached to a straight condenser, butyl bromide with an b.p. of 98° and n_D^{20} 1.4348 being driven off. The flask residue solidified into a porous white mass. The salt-ester was insoluble in absolute alcohol.

0.0745 g, 0.1007 g substance: 20.1 ml 27.2 ml NaOH (T = 0.2094). **Found %:** P 14.85, 14.95. **C$_7$H$_{16}$O$_4$PLi.** Calculated %: P 15.35.

Action of lithium iodide upon the dibutyl ester of ethoxymethylphosphinic acid. When 1.2 g of lithium iodide was heated with 2 g of the butyl ester of ethoxymethylphosphinic acid, the iodide dissolved and the reagents reacted together. Dissolution also took place at room temperature. A small quantity of liquid was distilled off at 140°. The residue solidified into a reddish hyaline mass, which was ground to a powder and washed with alcohol.

0.1417 g, 0.1805 g substance, 27.0, 37.0 ml NaOH (T = 0.2094). **Found %:** P 9.37, 9.27. **C$_{11}$H$_{25}$O$_4$IPLi.** Calculated %: P 8.03. **C$_7$H$_{16}$O$_4$PLi.** Calculated %: P 15.35.

The results of the reaction of sodium halides with the diisopropyl ester of ethoxymethylphosphinic acid are summarized in Table 3.

Action of sodium iodide upon the diisopropyl ester of ethoxymethylphosphinic acid. When 1.34 g of sodium iodide and 2 g of the isopropyl ester of ethoxymethylphosphinic acid were heated together to 180°, they interacted and were transformed into a homogeneous mass, which hardened upon cooling. The mass had a reddish color and deliquesced when exposed to the air.

0.2710 g, 0.1326 g substance: 43.9, 22.3 ml, NaOH (T = 0.01998). **Found %:** P 8.91, 9.34. **C$_9$H$_{21}$O$_4$IPNa.** Calculated %: P 8.30.

Action of lithium chloride upon the diisopropyl ester of ethoxymethylphosphinic acid. When 0.38 g of lithium chloride and 2 g of the isopropyl ester of ethoxymethylphosphinic acid were heated together to 80-85°, the chloride dissolved and reacted, producing a homogeneous white mass. The reaction product was hygroscopic.

0.0792 g, 0.1560 g substance: 15.5 ml, 34.3 ml, NaOH (T = 0.01998). **Found %:** P 12.23, 12.16. **C$_9$H$_{21}$O$_4$ClPLi.** Calculated %: P 11.63.

The addition product was heated to 150-160° with a straight condenser. A liquid with a b.p. of 35-36°, the boiling point of isopropyl chloride, was distilled off. The residue was a white mass, which was washed with alcohol and analyzed.

0.0718 g, 0.0886 g substance: 21.1 ml, 25.75 ml NaOH (T - 0.01998). **Found %:** P 16.26, 16.07. **C$_6$H$_{14}$O$_4$PLi.** Calculated %: P 16.49.

Action of lithium bromide upon the diisopropyl ester of ethoxymethylphosphinic acid. When 1.6 g of lithium bromide was heated to 85-90° with 3 g of the isopropyl ester of ethoxymethylphosphinic acid the reagents interacted, yielding an addition product. The hyaline mass deliquesced in air.

0.2468 g, 0.2332 g substance: 47.0 ml, 43.0 ml NaOH (T - 0.2094). **Found %:** P 10.50. 10.02. **C$_9$H$_{21}$O$_4$BrPLi.** Calculated %: P 10.0

The addition product was heated to 180-190°. Isopropyl bromide, with a b.p. of 58-59°, n_D^{20} 1.4198, which agree with the figures in the literature, was distilled. The residue was a white porous mass, which was washed with absolute alcohol and analyzed.

· 0.0968 g, 0.1530 g substance: 28.5 ml, 43.9 ml NaOH (T = 0.02094). **Found %:** P 16.34, 15.9. **C$_6$H$_{14}$O$_4$PLi.** Calculated %: P 16.49.

Action of sodium bromide upon butyl phosphate Equimolecular quantities of sodium bromide and butyl phosphate were heated to 170-200°. We then distilled off a liquid product with a b.p. of 101°, which is that of butyl bromide. The residue in the flask solidified into a porous white mass. The residue was purified by dissolving it in absolute alcohol.

0.0736 g substance: 18.8 ml NaOH (T = 0.01779). **Found %:** P 12.58. **C$_8$H$_{18}$O$_4$PNa.** Calculated %: P 13.35.

SUMMARY

1. The halides of lithium, sodium, and potassium react with esters of alkyl-phosphinic acids whenever the alkyl radical contains a polar group, yielding salt-esters of these acids.

2. The velocity of the reaction of the halides with the esters of alkylphosphinic acids depends upon the nature of the metal, the halogen, and the ester radical.

3. The addition products of lithium chloride and bromide to esters of alkylphosphinic acids have been isolated, thus establishing the mechanism involved in these reactions.

4. Sodium halides react with butyl phosphate.

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THE REACTION OF SOME PHOSPHORUS HALIDES

WITH ESTERS OF GLYCOLIC ACID

A.Razumov, V.Kukhtin, and N.Sazonova

The reaction of phosphorus halides with alcohols has been extensively investigated and is a matter of common knowledge. In particular, when phosphorus trichloride or tribromide is reacted with alcohols, we get satisfactory yields of neutral or acid esters of phosphorous acid, depending upon the conditions. As in the case of phosphorus trichloride, the reaction of other halogen compounds of phosphorus of the following types: $ArPCl_2$; Ar_2PCl; $(RO)PCl_2$; and to a lesser extent, of the $(RO)_2PCl$ type, has been investigated [1-7]. But alongside this, we have practically no knowledge of the reaction of the foregoing phosphorus halides with such hydroxyl compounds as the hydroxy acids, or, more precisely, their esters.

We know of only two brief references to such compounds in the existing literature. The paper by Cook, Saunders, and McCombie [8] gives an outline of the reaction between phosphorus trichloride and ethyl lactate, resulting in the production of di-(1-carbethoxyethyl)-phosphoric acid. The latter was then converted into the respective phenylamide of di-(1-carbethoxyethyl)-phosphoric acid by chlorinating it still further and then treating it with aniline. No other information is given, nor is any of the compounds identified. The other instance is that of Dietrich's patent, which mentions the production of the tricarbopropoxymethyl ester of phosphorous acid $P(OCH_2COOR)_3$. The ester is not identified in the patent, nor is any other information given [9].

We were interested in studying the reactions mentioned above, as well as the properties of the resulting compounds. We report the results of these investigations in the present paper.

The simplest representatives of the hydroxy acids were selected, namely the esters of glycolic acid. The halogen compounds of phosphorus employed were phosphorus trichloride, the alkoxydichlorophosphines $ROPCl_2$, and the dialkoxychlorophosphines $(RO)_2PCl$. We tried to synthesize a phosphite of the $P(OCH_2COOR)_3$ type by reacting an ester of glycolic acid with phosphorus trichloride and dimethylaniline in anhydrous ether.

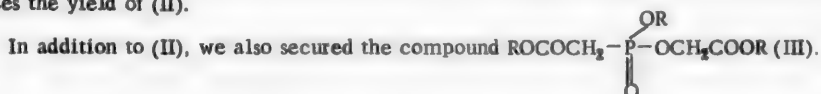$$PCl_3 + 3HOCH_2COOR + 3C_6H_5N(CH_3)_2 \rightarrow P(OCH_2COOR)_3 + 3C_6H_5N(CH_3)_2 \cdot HCl. \qquad (1)$$

In our first experiment, run at 30-35°, we were able to recover substantial quanties of nothing but the respective ester of chloroacetic acid. Nor were we able to secure the desired product in the next experiment, in which chilling was employed, though we did get its isomerization product, namely: $ROCOCH_2-PO(OCH_2COOR)_2$ (I) the yield being 45% of the theoretical. As a compound of pentavalent phosphorus, it did not react with bromine or with monovalent copper salts. We have established the composition of the compound and its properties. The production of an isomerization product may be explained in different ways. As we know, such isomerization processes can be brought about by thermal causes, but we believe it is more likely that this process is due to the formation of an ester of chloroacetic acid in the reaction medium.

Reacting the ester of glycolic acid with the dialkoxychlorophosphine yielded a normal product as follows:
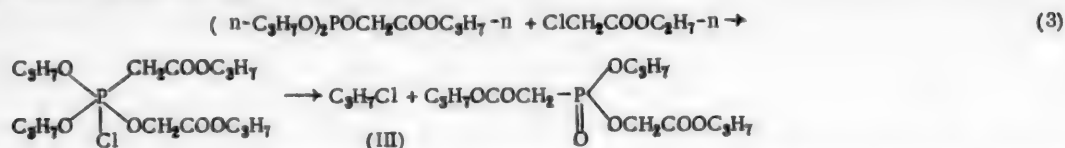
$$(RO)_2PCl + HOCH_2COOR + C_6H_5N(CH_3)_2 \rightarrow (RO)_2POCH_2COOR + C_6H_5N(CH_3)_2HCl. \qquad (2)$$
$$(II)$$
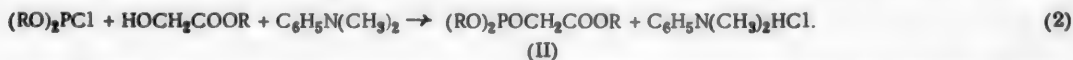
Using a lower temperature for the reaction and a higher vacuum when fractionating the resultant mixture increases the yield of (II).

In addition to (II), we also secured the compound $ROCOCH_2-\overset{\displaystyle OR}{\underset{\displaystyle O}{P}}-OCH_2COOR$ (III).

The compound (III) formed in a so-called Arbuzov rearrangement, can be produced only when the reaction medium contains an ester of chloroacetic acid, as we have demonstrated.

Compound (II) was processed under certain conditions with an ester of chloroacetic acid to provide more convincing proof of the structure of (III). As a compound with trivalent phosphorus, the compound (II) should enter into an Arbuzov rearrangement with the ester of chloroacetic acid, as follows:

$$(\ n\text{-}C_3H_7O)_2POCH_2COOC_3H_7 \text{-}n \ + ClCH_2COOC_2H_7\text{-}n \rightarrow \tag{3}$$

$$\longrightarrow C_3H_7Cl + C_3H_7OCOCH_2-P$$

(III)

As a matter of fact, this product was isolated and its properties proved to be the same as those of (III). We also secured the compound (IV), in addition to the normal rearrangement product.

(IV)
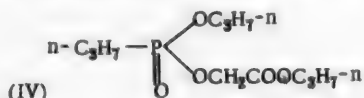
The only explanation for the production of (IV) is the formation of propyl chloride during the reaction pictured in (3). This chloride evidently enters into "competition" with the ester of chloroacetic acid, resulting in the formation of (IV) by an analogous reaction (Schema 3).

We also synthesized the product (II) by another method in order to explore the conditions governing its formation and yield. By analogy with the A.E.Arbuzov method for alcoholates of alcohols [10], we prepared a metallic derivative of an ester of chloroacetic acid and then reacted it with dialkoxychlorophosphine in ether as follows:

$$(RO)_2PCl + NaOCH_2COOR \rightarrow (RO)_2POCH_2COOR + NaCl. \tag{4}$$

Recovery of the substance requires repeated fractionation in this case as well, since a rather complex mixture is ordinarily produced in the reaction. The resulting substance has properties that are identical with those of (II), produced by the first method. As a compound with trivalent phosphorus, it reacts violently with bromine and also reacts with cuprous salts, though it does not constitute crystalline compounds. For the sake of comparing it with (II) we synthesized an isomeric compound with pentavalent phosphorus (V) in the following reaction:

$$(RO)_2PONa + ClCH_2COOR = (RO)_2P-CH_2COOR + NaCl. \tag{5}$$

(V)
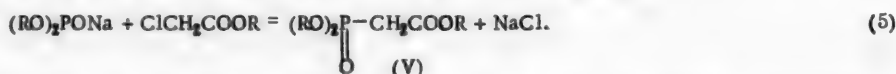
(V) differs pronouncedly from (II) and does not react with bromine, nor does it enter into reactions with cuprous salts.

We succeeded in securing a small quantity (about 10 g) of the normal reaction product, the composition of which was $C_2H_5O-P(OCH_2COOC_2H_5)_2$ (VI), by reacting ethyl glycolate with an alkoxydichlorophosphine. The composition and the purity of the isolated product were established by analysis and by its molar refraction. The product was subjected to an Arbuzov rearrangement by exposing it to the action of ethyl iodide, a very small quantity of the normal rearrangement product, $C_2H_5-PO(OCH_2COOC_2H_5)_2$ (VII), being recovered.

This research demonstrates that the ease with which chlorine can be substituted for a hydroxyl group and the formation of esters of chloroacetic acid both affect the course of the reaction. There is no doubt that chlorinating ability diminishes progressively in the following order: $PCl_3 \rightarrow ROCl_2 \rightarrow (RO)_2PCl$. It is therefore easier to secure a normal product with trivalent phosphorus by reacting an ester of glycolic acid with a dialkoxychlorophosphine, $(RO)_2PCl$; this procedure likewise gave us the highest yield. The yield of the product with an alkoxydichlorophosphine was much lower, while the reaction with phosphorus trichloride yielded nothing but a product in an isomeric state.

EXPERIMENTAL

Reaction of Phosphorus Trichloride with Ethyl Glycolate

1. 39 g of the ethyl ester of glycolic acid, 55 g of dimethylaniline, and anhydrous ether as a solvent were placed in a flask fitted with a stirrer, a reflux condenser and a thermometer, and the mixture was chilled with snow while 18 g of phosphorus trichloride was added. The temperature of the reaction mass was 30-32°. After all the phosphorus trichloride had been added, the mass was refluxed for 30 minutes, the ether boiling gently. The dimethylaniline hydrochloride was filtered out, the ether driven off, and the product fractionated. Red phosphorus settled out at a bath temperature of approximately 120°, and a liquid with a b.p. of 40-42° at 15 mm was distilled off, which proved to be ethyl chloroacetate.

2. 39 g of ethyl glycolate and 46 g of dimethylaniline were placed in the same type of flask as that used in the first test, and 17.5 g of phosphorus trichloride was added. Anhydrous ether was used as the solvent. The reaction was run at a temperature of $\div5$ to $-10°$, in contrast to the first test, with fractionation performed at 0.5 mm vacuum. Triple fractionation yielded a fraction with a boiling point of 156-158° at 0.5 mm — a colorless liquid with a faint, characteristic odor. The yield was 18 g (43% of the theoretical). The product did not react with a cuprous halide, nor did it decolorize bromine. It reacted readily with metallic sodium.

d_0^{20} 1.2134; n_D^{22} 1.4405; MR_D 73.91; calculated 73.34.

0.1183 g substance: 18.70 ml NaOH. 0.1643 g substance: 27 ml NaOH (1 ml NaOH = 0.0005707 g P).
Found %: P 9.03, 9.37; $C_{12}H_{21}O_9P$. Calculated % P: 9.12.

Analysis indicated that the product was the compound (I).

Synthesis of dipropyl-(carbopropoxymethyl) phosphite. For the purposes of this synthesis we prepared di-n-propoxychlorophosphine by a method worked out in our laboratory [11,12], and the n-propyl ester of glycolic acid. The latter was prepared, in accordance with the references in the literature, from propyl chloroacetate and sodium glycolate [13]. We prepared the ester by reacting n-propyl alcohol with glycolic acid in the presence of sulfuric acid, using 5 g of sulfuric acid to 19 g of glycolic acid and 55 g of the alcohol. The mixture was refluxed for 6-7 hours, after which the sulfuric acid was neutralized with potash, and the precipitated potassium sulfate filtered out. The residual potassium salt was thrown down by adding ether and then refiltered out. This yielded 17 g (58% of the theoretical). B.p. 63.2-63.5° at 12 mm; d_4^0 1.0725; d_{13}^{18} 1.0563; n_D^{18} 1.4138. The ester was analyzed, because of the discrepancies in the physical constants cited in the literature. Found %: C 50.38; H 8.64; $C_5H_{10}O_3$. Calculated %: C 50.84; H 8.47. The analysis of the product and the steady boiling point are indisputable proof of the high purity of the product.

The ester was synthesized in the same vessel as that used in the preceding experiment. For the reaction we took 12.5 g of the n-propyl ester of glycolic acid and 13 g of dimethylaniline in anhydrous ether, chilling the mixture to −5 to −10°, and adding 19 g of dipropoxychlorophosphine diluted with anhydrous ether. Double fractionation yielded two fractions. Fraction 1 was a colorless liquid with the typical odor of a phosphite. B.p. 139-140° at 8 mm, 116-117° at 0.25 mm. It reacted violently with bromine. It entered into reaction with cuprous salts, evolving considerable heat, but no crystalline products were formed.

d_0^{20} 1.001; n_D^{22} 1.4267; MR_D 68.03; calculated 67.81.

0.2113 g substance: 45.8 ml NaOH. 0.1666 g substance: 36.6 ml NaOH (1 ml NaOH = 0.0005707 g P).
Found % P: 11.90, 11.83; $C_{11}H_{23}O_5P$. Calculated %: P 11.66.

Thus, its analysis, molar refraction, and properties all are evidence that this is the normal product (II). The product yield is increased by using a higher vacuum during fractionation, 9.3 g (27% of the theoretical) being obtained in the second experiment.

Fraction 2 was a colorless, nearly odorless liquid. B.p. 150-152° at 15 mm. It does not decolorize bromine nor does it react with a cuprous salt.

d_0^{20} 1.1051; n_D^{20} 1.4398; MR_D 76.90; calculated 76.40.

0.2097 g substance: 37.6 ml NaOH. 0.1852 g substance: 32.97 ml NaOH (1 ml NaOH = 0.0005707 g P).
Found %: P 10.16, 10.26. $C_{12}H_{25}O_7P$. Calculated %: P 9.56.

The analysis, molar refraction, and properties of this fraction indicate that it is the compound (III).

Rearrangement. 9 g of the phosphite (II) was placed in a sealed tube with 5 g of the n-propyl ester of glycolic acid and heated to 140° for 4 hours. This resulted in a considerable diminution of the liquid in the tube. The change in volume ceased after 5 hours, and heating was stopped. Two fractions were collected in vacuum fractionation.

Fraction 1 was a colorless, nearly odorless liquid, which did not react with bromine. It weighed 2 g (22% of the theoretical). B.p. 154-155° at 2.5 mm.

d_0^{20} 1.0627; n_D^{20} 1.4350; MR_D 65.36; calculated 65.32.

0.1164 g substance: 23.0 ml NaOH. 0.1450 g substance: 29.3 ml NaOH (1 ml NaOH = 0.0005707 g P).
Found %: P 11.29, 11.53. $C_{11}H_{25}O_5P$. Calculated %: P 11.66.

The analysis, molar refraction, and properties of this substance were those of the compound (IV).

Fraction 2 was a colorless, nearly odorless liquid, which did not react with bromine. The yield was 4 g (38% of the theoretical). B.p. 176-177° at 2.5 mm.

d_0^{20} 1.1059; n_D^{20} 1.4392.

0.1162 g substance: 19.57 ml NaOH (1 ml NaOH = 0.0005707 g P). Found %: P 9.56. $C_{13}H_{25}O_7P$. Calculated %: P 9.56.

The analysis and the constants indicated that we had secured the normal rearrangement product (II).

Synthesis of dipropyl-(carbopropoxymethyl) phosphite via a metallic derivative of ethyl glycolate. An alcoholate was prepared from 4.7 g of sodium and 75-80 g of n-propyl alcohol, and 23.8 g of n-propyl glycolate was added to it. The alcohol was driven off, first at ordinary pressure, and then by the A.E. Arbuzov method; the sodium derivative "swelled up." It should be noted that this swelling is not as satisfactory as in the alcoholates of the simpler alcohols.

Anhydrous ether was added to the sodium derivative, and the mixture was stirred and chilled while 38 g of dipropoxychlorophosphine was gradually added. After all the phosphine had been added, the mass was heated for one hour; then the sodium chloride was filtered out, the solvent driven off, and the ester distilled in vacuo.

Triple fractionation yielded a fraction with a b.p. of 139-141° at 6 mm.

d_0^8 1.0492; $n_D^{20.5}$ 1.4261.

0.1135 g substance: 27.25 ml NaOH. 0.1374 g substance: 32.40 ml NaOH (T = 0.01848) Found %: P 11.91, 11.70. $C_{11}H_{23}O_5P$. Calculated %: P 11.65.

It reacted actively with bromine like a trivalent phosphorus compound, 0.2 g of the ester using up 1.13 g of bromine (until the color was a light yellow). Theoretically 0.12 g of bromine was required. 0.5 g of the ester was mixed with 0.36 g of CuI (1:1). The mass warmed up considerably (45°), but yielded no crystalline product, a thick, colorless liquid being formed.

The analysis, physical constants, and behavior of this product indicate that it is the same as the compound (II) described above.

Synthesis of the ester (V). The ester was preparing by reacting the sodium derivative of dipropylphosphorous acid with n-propyl chloroacetate. We took 37.5 g of dipropylphosphorous acid, 7 g of metallic sodium, and 40.65 g of the chloroacetate for this reaction, which was carried out in a solution of anhydrous ether. Filtering out the sodium chloride and driving off the solvent yielded 70 g of the crude product (88% of the theoretical). Fractionation yielded the ester with a b.p. of 142.5-143° at 3 mm.

n_D^{20} 1.4279.

0.1311 g substance: 28.3 ml NaOH. 0.1373 g substance: 29.8 ml NaOH (T = 0.019946). Found %: P 11.26, 11.32. $C_{11}H_{23}O_5P$. Calculated %: P 11.65

The ester behaves like a pentavalent phosphorus compound, turning dark red with a single small drop of bromine, and failing to react with a cuprous halide. The reaction with metallic sodium is vigorous.

Reaction of ethyl glycolate with ethoxydichlorophosphine. 48 g of ethyl glycolate, 73 g of dimethylaniline, and 500 ml of absolute ether were placed in a 1-liter three-necked flask, fitted with a reflux condenser, a stirrer, and a dropping funnel; the flask was chilled with a freezing mixture.

34 g of ethoxydichlorophosphine, diluted with anhydrous ether, was slowly added a drop at a time from the dropping funnel, the temperature within the reaction flask being kept at −10°. After the reaction was over, the dimethylaniline hydrochloride was eliminated and the solvent driven off. A large number of fractionations of the principal product, some of them performed with a Widmer column, yielded a fraction with a b.p. of 146° at 2.0 mm, the yield being 9.4 g, or 14.8% of the theoretical.

A colorless, highly mobile liquid with a peculiar odor, insoluble in water, and reacting violently with bromine.

d_0^{19} 1.1513; n_D^{19} 1.4412; MR_D 64.70; calculated 64.75.

0.1847 g substance: 32.8 ml NaOH. 0.1147 g substance: 21.2 ml NaOH (T = 0.0617). Found %: P 10.95, 10.40. $C_{10}H_{19}O_7P$. Calculated %: P 10.99.

Rearrangement. 8 g of the synthesized ester was sealed into a tube together with 4.5 g of ethyl iodide and heated to 140° for 4 hours. The product discovered after the tube was opened had a dark color; the color was lightened by processing the product with activated charcoal, after which it was distilled. A fraction with a b.p. of 2.5 mm, totaling 0.5 g, was collected. A difficultly mobile liquid with a singular odor, which does not react with bromine.

0.1770 g substance: 23.9 ml NaOH. 0.1613 g substance: 26.9 ml NaOH (T = 0.0684). Found %: P 11.32. $C_{10}H_{19}O_7P$, Calculated %: P 10.99. Found $\underline{M}$ 262, 272 (Rast).   Calculated: $\underline{M}$ 282.

SUMMARY

1. The reaction of esters of glycolic acid with phosphorus trichloride, ethoxydichlorophosphine, and dipropoxychlorophosphine has been explored.

2. It has been found that when phosphorus trichloride is reacted with the ethyl ester of glycolic acid, we get an isomer containing pentavalent phosphorus (I), instead of the normal product $P(OCH_2COOC_2H_5)_3$ containing trivalent phosphorus. An explanation is provided for this phenomenon.

3. Dipropyl-(carbopropoxymethyl) phosphite (II) has been synthesized by two methods.

4. It has been established that the dipropyl-(carbopropoxymethyl) phosphite is partially rearranged to a compound with pentavalent phosphorus (III) during the synthesis.

5. The dipropyl-(carbopropoxymethyl) phosphite has been rearranged by the action of a chloroacetate, thus effecting the synthesis of (III). This synthesis has established the structure of the ester, secured as a by-product of the synthesis of dipropylcarbopropoxymethyl phosphite.

6. It has been established that rearrangement of the dipropyl-(carbopropoxymethyl) phosphite yields another product (IV), in addition to the normal product (III). An explanation is advanced for the formation of (IV), and its composition has been established.

7. Seven compounds of a new type, not previously described in the literature, have been synthesized during this research.

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RESEARCHES ON BISULFITE COMPOUNDS

XVI. THE BISULFITE COMPOUND OF 1-AMINO-8-NAPHTHOL-2,4-DISULFONIC ACID

V.N. Ufimtsev and M.I. Chernyak

When 1-amino-8-naphthol-2,4-disulfonic acid is heated with solutions of sodium or potassium bisulfite, the reactions that are typical of this aminoaphthol sulfo acid quickly disappear, and its bisulfite compound is formed. It is impossible to forecast the direction taken by the reaction or the structure of the compound formed, since both the amino and the hydroxy groups attached to the naphthalene nucleus can react with the bisulfite. Moreover, the amino group at the 1 position is exposed to the activating influence of the sulfo group at the 4 position, on the one hand, and to the deactivating influence of the sulfo group at the 2 position on the other [1]. N. N. Vorozhtsov, Sr. [2] states that when 2,4-(bisbenzeneazo)-1-naphthol is heated with sodium bisulfite, which constitutes an analogous case, the bisulfite compound is produced normally.

After the heating of 1-amino-8-naphthol-2,4-disulfonic acid with bisulfites was complete, the resulting solution was found to contain a small amount of the initial product and larger quantities of mineral salts (the sulfite, the bisulfite, and the sulfate), in addition to the expected bisulfite compound. We utilized the method of precipitating the sulfates and sulfites with a barium carbonate solution, described previously [3], to purify the product. Evaporating the resultant filtrates threw down the sodium and potassium salts of the bisulfite compound (it being much easier to recover and purify the potassium salt), which upon analysis proved to contain nitrogen, with one molecule of the bisulfite added to the molecule of 1-amino-8-naphthol-2,4-disulfonic acid. Of the two possible formulas:
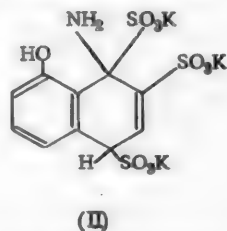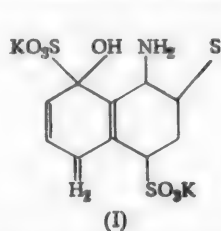
(I) represents the structure of the synthesized bisulfite compound, since the latter is incapable of coupling with diazonium compounds, whereas it is readily diazotized by treatment with a nitrite in an acid medium, after which it forms dyes by coupling with various azo constituents, i.e., it contains an amino group attached to the aromatic portion of the ring.

EXPERIMENTAL

1. Sodium salt of the bisulfite compound of 1-amino-8-naphthol-2,4-disulfonic acid. 140 grams of the 51% monopotassium salt of 1-amino-8-naphthol-2,4-disulfonic acid (= 71.4 g of the 100% product = 0.2 mole) was refluxed with 25 ml of a 25% sodium hydroxide solution and 200 ml of a sodium bisulfite solution (sp. gr. 1.32) in a round-bottomed flask for 12 hours. The resultant solution was processed by carefully adding a concentrated solution of barium carbonate until the sulfate and sulfite ions were precipitated (no excess!), the precipitated insoluble barium salts being filtered out and washed with a little water. The filtrate was evaporated to 310 ml on a water bath and precipitated with 1120 ml of methanol; this yielded 32.1 g of a yellowish product, which is very readily soluble in water. Double recrystallization from water yielded 4.1 g of the slightly greenish crystalline sodium salt of the bisulfite compound.

0.1508 g, 0.1801 g substance: 0.0610 g, 0.0723 g Na_2SO_4. 0.1904 g substance: 0.0240 g H_2O. Found %: Na 13.10, 13.00; H_2O 12.60. $C_{10}H_8O_{10}S_3NNa_3$. $3\frac{1}{2}H_2O$. Calculated %: Na 13.01; H_2O 11.89.

2. Potassium salt of the bisulfite compound of 1-amino-8-naphthol-2,4-disulfonic acid. 140 grams of the 51% monopotassium salt of 1-amino-8-naphthol-2,4-disulfonic acid was refluxed for 12 hours in a round-bottomed

flask with 15 g of potassium hydroxide and 500 ml of a 20.5% potassium bisulfite solution. The solution was treated with barium carbonate as specified in the synthesis of the sodium salt. When the filtrate was evaporated to 300 ml and then cooled, a finely crystalline precipitate was thrown down; it was filtered out, washed with methanol and ether, and dried, its weight being 30.5 g. The synthesized substance was recrystallized twice from three times its weight of 50% methanol, washed with methanol and ether, and dried in a vacuum desiccator; colorless needles with blunted ends, weight 11.65 g.

0.1470 g, 0.1513 g, 0.1498 g substance; 0.0690 g, 0.0713 g, 0.0710 g K_2SO_4. 3.462 mg, 4.594 mg substance; 2.756 mg, 3.689 mg CO_2; 0.618 mg, 0.949 mg H_2O. 6.824 mg, 6.931 mg substance: 0.146 ml N_2 (21.8°, 736.3 mm), 0.152 ml N_2 (22°, 736.5 mm). Found %: K 21.06, 21.15, 21.27; C 21.72, 21.92; H 2.00, 2.31; N 2.40, 2.46. $C_{10}H_8O_{10}S_3NK_3 \cdot 2H_2O$. Calculated %: K 21.26; C 21.77; H 2.19; N 2.54.

The synthesized bisulfite compound is not coupled in a soda medium with solutions of phenyl- and p-tolyl-diazonium chlorides, nor does it give off sulfur dioxide when boiled with dilute sulfuric acid.

When its dilute solutions are heated with caustic alkalies, the bisulfite compound decomposes into a sulfite and the initial 1-amino-8-naphthol-2,4-disulfonic acid, exhibiting the following characteristic reactions: a) evolution of sulfur dioxide when acidulated with dilute sulfuric acid and then boiled; b) production of the brown solution of a diazo compound when acidulated and diazotized; c) coupling with diazoniums in soda, yielding the corresponding azo dyes.

When the bisulfite compound is diazotized, we get diazo compounds that couple readily with azo constituents in a soda medium, yielding dyes whose tones are perceptibly different from those of the analogous dyes produced by diazotizing and coupling the 1-amino-8-naphthol-2,4-disulfonic acid itself.

Azo constituent	Diazo constituent	
	1-Amino-8-naphthol-2,4-disulfonic acid	Its bisulfite compound
	Color of the dye solution	
2-Naphthol-6-sulfonic acid	Yellowish-brown	Yellowish-red
2-Naphthol-3,6-disulfonic acid	″ ″	Red
1-Amino-8-naphthol-2,4-disulfonic acid	Greenish-brown	Wine-red
1-Amino-8-naphthol-3,6-disulfonic acid	Orange-brown	Violet-red

The dyes prepared from the bisulfite compound of 1-amino-8-naphthol-2,4-disulfonic acid are decomposed when heated briefly with caustic alkalies, splitting off the bisulfite and thus being transformed into dyes that are identical with those synthesized from the 1-amino-8-naphthol-2,4-disulfonic acid itself by diazotizing it and coupling it with the corresponding azo constituents.

SUMMARY

When 1-amino-8-naphthol-2,4-disulfonic acid is treated with potassium or sodium bisulfite, its bisulfite compound is produced. In this reaction only one molecule of the bisulfite reacts with the hydroxy group; the amino group is not affected by the reaction, owing to the deactivating influence of the sulfo group at the 2 position of the naphthalene nucleus.

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Intermediates

THE REACTIONS OF GLYCIDOL AND ITS ETHERS WITH ACID AMIDES

IV. THE REACTIONS OF GLYCIDOL ETHERS WITH FORMAMIDE AND ACETAMIDE

F. G. Ponomarev

As we have shown in one of our previous reports [1], the methyl and ethyl ethers of glycidol react with formamide, yielding the N-mono- and N,N-disubstitution derivatives of formamide: HCONHCH₂–CHOH–CH₂OR and HCON(CH₂–CHOH–CH₂OR)₂. We later showed [2] that the reaction of these ethers with acetamide likewise involved the formation of two products:

CH₃CONH–CH₂–CHOH–CH₂OR and CH₃CON(CH₂–CHOH–CH₂OR)₂,

where (as in the first case) R = CH₃ and C₂H₅.

We naturally supposed that this reaction would follow the same course with the higher members of the homologous series of ethers. This was borne out by experiments that form the topic of the present report. Reacting the isopropyl ether of glycidol with the amides of formic and acetic acids and reacting the n-butyl ether with acetamide give rise to mono- and disubstitution derivatives of the amides:

HCONH–CH₂–CHOH–CH₂OC₃H₇ and HCON(CH₂–CHOH–CH₂OC₃H₇)₂,
CH₃CONH–CH₂–CHOH–CH₂OR and CH₃CON(CH₂–CHOH–CH₂OR)₂,
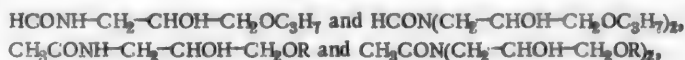
where R = iso-C₃H₇ and n-C₄H₉. The principal product was the monosubstituted amide in every instance. The percentages of the disubstituted amide were lower, which is only natural, as it is formed from the monosubstituted product by the reaction of the latter with new molecules of the ether.

These results justify us in the assumption that the action of glycidol ethers upon acid amides, resulting in the simultaneous formation of two products, is a universal reaction in the glycidol ether series. It is worthy of note that as the molecular weight of the glycidol ethers rises, their ability to react with acid amides diminishes. Of the four ethers investigated under identical conditions, the methyl ether of glycidol reacts most easily with the amides of formic and acetic acid. This is proved by the fact that the aggregate yield of the N-mono- and N,N-disubstituted products exceeds 65% when the methyl ether is reacted with formamide and acetamide, while the product yield of the reaction of the ethyl, isopropyl, and n-butyl ethers of glycidol with these amides is 37-40%, based on the ether.

The isopropyl and n-butyl ethers do not react with formamide or acetamide under ordinary conditions, so that the reaction mixture had to be heated to 150° for 10 hours and sodium hydroxide had to be employed as a catalyst. It is worthy of note that ammonia and amines react rather energetically with these same four glycidol ethers even at room temperature.

The constants of the synthesized substances are given in Table 1.

TABLE 1

Substance	Boiling point (at 4 mm)	d_4^{15}	n_D^{15}	MR$_D$ Calculated	MR$_D$ Experimental
HCONH–CH₂–CHOH–CH₂–O–CH(CH₃)CH₃	122-127°	1.0721	1.4570	41.07	40.95
HCON(CH₂–CHOH–CH₂–O–CH(CH₃)CH₃)₂	202-208	1.0677	1.4620	72.39	71.42
CH₃CONH–CH₂–CHOH–CH₂–O–CH(CH₃)CH₃	90-93	1.0428	1.4435	45.69	44.63
CH₃CON(CH₂–CHOH–CH₂–O–CH(CH₃)CH₃)₂	198-205	1.0215	1.4462	77.01	76.05
CH₃CONHCH₂–CHOH–CH₂–O–(CH₂)₃–CH₃	110-114	1.0151	1.4410	50.31	49.26
CH₃CON[CH₂–CHOH–CH₂–O–(CH₂)₃CH₃]₂	206-210	1.0011	1.4451	86.31	84.94

acetamide, 12.5 g of the ether (20% excess), and 3 drops of conc. H_2SO_4 were heated together in a sealed glass tube to 150° on an oil bath for 10 hours. The reaction mixture was chilled to −10° to eliminate the unreacted acetamide, and then after part of the amide had been removed, the mixture was processed three times with 15-ml portions of absolute ether; this processing yielded a total of 1.3 g (24%) of the unchanged acetamide. After the ether had been driven off on a water bath, the reaction product was fractionated in vacuo twice. This yielded 4 g (21.2%) of N-propanol-2-isopropoxy-3-acetamide and 3.1 g (19.8%) of N,N-di-(propanol-2-isopropoxy-3)-acetamide. In the flask there remained 0.6 g of a tacky polymer. The same two products were formed in tests run under similar conditions, but without utilizing NaOH as a catalyst, though the yields were lower.

a) 2.3 g of acetamide and 5.4 g of the ether yielded 1.3 g (16%) of the N-monosubstituted acetamide and 0.7 g (10.4%) of the N,N-disubstituted acetamide.

b) 5 g of acetamide and 12 g of the ester yielded 2.5 g (13.8%) and 1.5 g (9.9%) of the respective reaction products.

The aggregate yield of reaction products was 23-26% in the tests in which no catalyst was used, and 40% in the tests that employed NaOH as a catalyst. The unchanged acetamide recovered totaled 24% in the tests using a catalyst and 50% in the tests without one.

The resultant products — the N-mono- and the N,N-disubstituted acetamides — were colorless or faintly colored, oily liquids with a specific odor, which were freely soluble in alcohol, ether and acetone, and sparingly so in water.

Analysis of N-propanol-2-isopropoxy-3-acetamide.

0.0928 g substance: 5 ml 0.1 N H_2SO_4. 0.1082 g substance: 5.81 ml 0.1 N H_2SO_4. 0.1674 g substance: 9.33 ml 0.1 N NaOH. 0.0938 g substance: 5.29 ml 0.1 N NaOH. Found %: N 7.60, 7.52; OH 9.47, 9.58. $C_8H_{16}O_2N(OH)$. Calculated %: N 7.99; OH 9.70.

2.5 g of N-propanol-2-isopropoxy-3-acetamide was oxidized with sodium dichromate, yielding 1 g of an oily liquid with a b.p. of 79-84° at 7 mm; n_D^{20} 1.440, which exhibited a positive reaction for a carbonyl group with phenylhydrazine.

Analysis of N,N-di-(propanol-2-isopropoxy-3)-acetamide.

0.1206 g substance: 3.87 ml 0.1 N H_2SO_4. 0.1138 g substance: 3.77 ml 0.1 N H_2SO_4. 0.1554 g substance: 11 ml 0.1 N NaOH. 0.1230 g substance: 8.78 ml 0.1 N NaOH. Found %: N 4.41, 4.63; OH 12.03, 12.13. $C_{14}H_{27}O_3N(OH)_2$. Calculated %: N 4.81; OH 11.68.

5. Reaction of glycidyl n-butyl ether with acetamide (together with L. N. Khopina). Reacting 4 g of acetamide with 10.6 g of the ether (20% excess) and 3 drops of conc. NaOH under the conditions described above yielded 4 g (25.9%) of N-propanol-2-butoxy-3-acetamide and 1.5 g (11.5%) of N,N-di-(propanol-2-butoxy-3)-acetamide. The unchanged acetamide that was recovered totaled 26%. The distilling flask contained a residue of 1.3 g of a tacky polymer.

The synthesized substances were slightly yellowish, oily liquids with a specific odor, freely soluble in alcohol and ether, slightly so in water, and insoluble in benzene.

Analysis of N-propanol-2-butoxy-3-acetamide.

0.1958 g substance: 9.18 ml 0.1 N H_2SO_4. 0.1684 g substance: 8.16 ml 0.1 N H_2SO_4. 0.1312 g substance: 6.2 ml 0.1 N NaOH. 0.1768 g substance: 8.57 ml 0.1 N NaOH. Found %: N 6.56, 6.78; OH 8.03, 8.24. $C_9H_{18}O_2N(OH)_2$ Calculated %: N 7.40; OH 8.98.

2 g of N-propanolbutoxyacetamide was distilled in vacuo over 1 g of $KHSO_4$, yielding 0.8 g of a substance with a b.p. of 100-105° at 8 mm; n_D^{20} 1.430. Brominating this substance in chloroform yielded 0.6 g of a colorless viscous oil, which crystallized in the receiver. The crystals fused at about 36°, exhibited a qualitative reaction for   bromine, and contained nitrogen.

0.1016 g substance: 3.26 ml 0.1 N H_2SO_4. Found %: N 4.49. $C_4H_{17}O_2Br_2N$. Calculated %: N 4.23.

These figures indicate that under the conditions described the N-propanolbutoxyacetamide is dehydrated by anhydrous $KHSO_4$ to a product with a double bond, which yields upon bromination a dibromide, the apparent structure of which is : CH_3−CONH−CHBr−CHBr−CH_2−O−$(CH_2)_3$−CH_3. The substance was not analyzed further because of the small quantities available.

<u>Analysis of N,Ni-di-(propanol-2-butoxy-3)-acetamide.</u>

0.1296 g substance: 3.57 ml 0.1 N H_2SO_4. 0.1554 g substance: 4.39 ml 0.1 N H_2SO_4. 0.2110 g substance: 12.67 ml 0.1 N NaOH. 0.1798 g substance: 10.91 ml 0.1 N NaOH. Found %: N 3.85, 3.95; OH 10.20, 10.31. $C_{16}H_{31}O_3N(OH)_2$. Calculated %: N 4.38; OH 10.65.

The polymer, formed, as indicated, in the reaction of the foregoing ethers with the acid amides, is a tarry substance that is freely soluble in alcohol and ether and sparingly so in water. Upon standing it is converted into a semisolid product that contains 3.2-3.7% of nitrogen.

SUMMARY

1. A study has been made of the reaction of glycidyl isopropyl ether with the amides of formic and acetic acid and the reaction of the n-butyl ether with acetamide.

2. It has been shown that in this reaction N-mono- and N,N-disubstituted amides are formed simultaneously in this reaction, the N-monosubstituted amide being the principal product.

3. The products of these reactions have been isolated and identified: N-propanol-2-isopropoxy-3-formamide, N,N-di-(propanol-2-isopropoxy-3)-formamide, N-propanol-3-isopropoxy-3-acetamide, N,N-di-(propanol-2-isopropoxy-3)-acetamide, N-propanol-2-butoxy-3-acetamide, and N,N-di(propanol-2-butoxy-3)-acetamide.

4. It has been found that the reactivity of the glycidol ethers with formamide and acetamide diminishes as their molecular weight is increased.

5. It has been noted that boron fluoride is a better catalyst than H_2SO_4 in the addition reactions of isopropyl and n-butyl alcohols to epichlorohydrin.

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STRUCTURAL CHANGES OF RUBBER CAUSED BY THE ACTION OF MOLECULAR OXYGEN

V. THE DESTRUCTIVE DISSOLUTION OF VULCANIZED SYNTHETIC RUBBERS

Z. Tarasova and B. Dogadkin

We have previously described [1,2] the process involved in the destructive dissolution of vulcanized natural rubber and the properties of the products formed as a result of this process. We showed that the vulcanized rubber does not dissolve when heated to 140° in hydrocarbon media or when acted upon by peptizers and polarizing substances added to the solvent provided oxygen is rigorously excluded. Only when molecular oxygen is present does heating cause the vulcanized rubber to enter the solvent medium, the process involving the following stages: addition of oxygen → breakdown of the molecular chains at the points where the oxygen has been added → dissolution. When the surface area of the vulcanized rubber remains unchanged, the process continues at a constant rate, depending upon the temperature and the oxygen partial pressure above the solvent. In the general case the variation of the rate of destructive dissolution with the oxygen partial pressure, $\frac{dKa}{d\tau}$, is expressed by the equation:

$$\frac{dKa}{d\tau} = K\frac{\gamma P}{\gamma P + 1},$$

where K and γ are constants.

The broken-down vulcanized rubber has a rather low molecular weight (3600 by the Lamm method), exhibits a Rayleighian scattering of light, and obeys the Einstein viscosimetric equation within a wide range of concentrations. This indicates that massive particles that are envelopes of the vulcanized rubber's space lattice enter solution during destructive dissolution.

The present paper describes the results of experiments that indicate that the phenomenon of destructive dissolution also takes place in synthetic vulcanized rubbers.

1. Effect of the nature of the rubber upon the kinetics of the destructive distillation of vulcanized rubber. Vulcanized sodium-butadiene rubber, butadiene-styrene rubber, chloroprene rubber, and butyl rubber were dissolved.

The vulcanized films were prepared from a benzene cement, applied to the surface of a glass ampoule, using the procedure described previously [1]. The composition of the vulcanized rubbers made of the sodium-butadiene and the butadiene-styrene rubbers was as follows: rubber—100.0; sulfur —2.0; thiuram —0.3; zinc oxide —1.0; and stearic acid —1.0. Optimum vulcanization was obtained in 30 minutes at 143°.

The chloroprene rubber (neoprene) was vulcanized from a mixture of the following composition: rubber — 100.0; magnesium oxide —3.0; rosin —3.0; and zinc oxide —3.0. This mixture was dissolved in dichloroethane. The optimum vulcanization was obtained in 30 minutes at 143°.

The vulcanized butyl rubber had the following composition: rubber —100.0, sulfur —2 0; thiuram —1.0; zinc oxide —2.0; and stearic acid —2.0.

The vulcanized films had mechanical characteristics that were typical for standard rubbers of the foregoing composition. It should be borne in mind that the composition of the vulcanized films prepared from the same paste changes somewhat with time, due to the settling of the insoluble ingredients. That is why comparable tests were made with films that had been produced at the same time.

Heating films of vulcanized sodium—butadiene rubber to 140° in xylene, with oxygen carefully excluded, caused no perceptible dissolution. The vulcanized synthetic rubbers mentioned above, however, dissolved completely when heated in a solvent that was saturated with molecular oxygen.

The procedure used for the experiments on destructive dissolution has been described earlier [1]. The
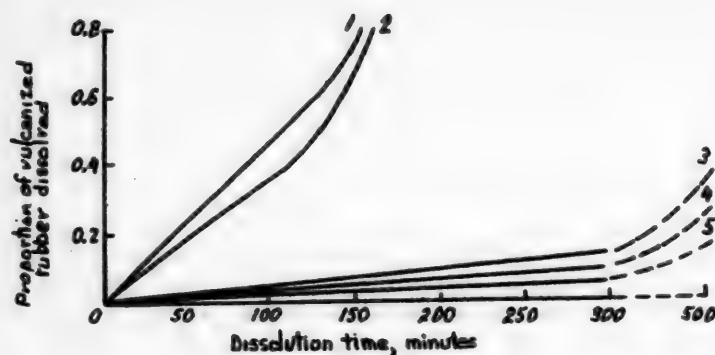
Fig. 1. Kinetic curves of the destructive dissolution of vulcanized rubbers. Temperature 110°, oxygen pressure approx. 760 mm Hg.

1) Natural rubber; 2) chloroprene rubber (neoprene); 3) butadiene—styrene rubber; 4) sodium—butadiene rubber; 5) butyl rubber.

kinetics of the destructive dissolution of vulcanized rubbers (Figure 1) are represented by curves of the same type, which exhibit a straight-line section at the start, corresponding to the period during which the area of the reaction surface remains constant. After this section of the curves the reaction rate rises sharply, owing to an increase in the surface, due to the mechanical destruction of the film and the slippage of its particles into the solution, which results in the uncovering of new parts of the surface. In conformity with the foregoing, the entire process of the destructive dissolution of a finely milled rubber is represented by a straight line. We rejected such procedure, however, since the surface area of a rubber proves to differ even with the most thorough milling.

As we might have expected, the rate of destructive dissolution depends upon the molecular structure of the rubbers (Table 1). The vulcanized rubbers may be arranged in the following order of increasing rate of destructive dissolution: butyl rubber < sodium—butadiene rubber < butadiene—styrene rubber < chloroprene rubber < natural rubber. In the case of rubbers whose molecules do not contain polar groups, this series corresponds to the concentration of double bonds in the principal chains of the polymer. The presence of polar groups retards the process of oxidative destruction. Thus, the vulcanized chloroprene rubber dissolves more slowly than the vulcanized natural rubber, although there are as many double bonds in the molecular chains of both rubbers. The slower dissolution of vulcanized butadiene rubbers may be due to peculiarities in the structure of these rubbers.

TABLE 1

Variation of the Rate of Destructive Dissolution of Vulcanized Rubbers with the Composition and Structure of the Rubber

No.	Rubber	Test temp. (°C)	% of 1,4 structure	Rate of destructive distillation, $\frac{g}{cm^2 \cdot min}$
1	Smoked sheets...........	110°	100	$4.95 \cdot 10^6$
2	Chloroprene (neoprene)	110	100	$3.8 \cdot 10^6$
3	Butadiene—styrene......	110	—	$4.0 \cdot 10^6$
4	Sodium—butadiene.....	110	43	$3.2 \cdot 10^6$
5	Butyl rubber..............	110	100	$3.0 \cdot 10^6$
6	Smoked sheets...........	120	100	$6.75 \cdot 10^5$
7	Butadiene................	120	59	$2.7 \cdot 10^5$
8	Butadiene................	120	54	$1.1 \cdot 10^5$
9	Butadiene................	120	43	$0.62 \cdot 10^5$

The dissolution of vulcanized rubbers when they are heated to temperatures that exclude thermal destruction in a solvent saturated with oxygen is caused by the fact that the reaction of the oxygen with the molecular chains of the spatial structure of the vulcanized rubber is accompanied by a breakdown of the latter at the double bonds, followed by the entrance of the detached particles into the solution. The molecules of natural rubber and of chloroprene rubber are so constructed that the monomer groups are connected into a linear chain at the 1,4 positions. It may be assumed with considerable probability that each act of oxidation and decomposition at the double bonds results in breaking the chain and diminishing the molecular weight. The monomer groups are connected at the 1,4 and 1,2 positions in the molecules of sodium—butadiene and butadiene—styrene rubbers, respectively. The double bonds exist in the main chain as well as in the vinyl side groups there being about 40% of the 1,4-type bonds and about 60% of structures of the 1,2 type in sodium—butadiene rubber.

It is quite obvious that the oxidation and breakdown of the double bonds in the vinyl side groups do not result in the breakdown of the spatial structure that is characteristic of the vulcanizate. Moreover, as Dogadkin has shown [4], the action of oxygen upon the vinyl side groups is responsible for the process of structuralization, inasmuch
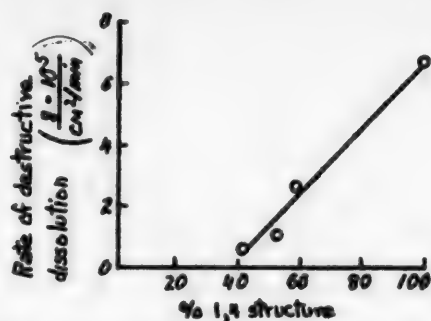
Fig. 2. Variation of the rate of destructive dissolution of vulcanized butadiene rubbers with the percentage of 1,4 structures. Temperature 120°; oxygen pressure approx. 760 mm Hg.

as the oxidation of the side vinyl groups gives rise to polyfunctional molecular chains (without diminishing the initial molecular weight), the oxygen groups of which can interact with one another and with the polymer's double bonds, giving rise to chemical and local intermolecular (hydrogen, orientation) bonds. When we add the possibility of the existence of polymerization processes, brought about by the action of peroxide compounds and—at high temperatures —by the action of heat, we begin to understand why the effectiveness of the destructive action of oxygen is greatly diminished in vulcanized rubbers made of butadiene polymers that contain vinyl side groups. The significance of different positions of the double bonds in the molecular chains of rubber during destructive dissolution is clearly shown in the butadiene polymers that contain varying proportions of the 1,4 and 1,2 structures.

We used rubbers that contained 59, 54, and 43% of the 1,4 structure according to the kinetics of the reaction with perbenzoic acid (the Prilezhayev reaction). The vulcanized rubbers were all prepared from the same recipe using a vulcanized natural rubber in which the percentage of the 1,4 structure was assumed to be 100%. We see in Figure 2 that the rate of destructive dissolution of these vulcanized rubbers is a linear function of the percentage of double bonds in the principal chains (1,4 structures). The fact that the straight line representing the rate of dissolution as a function of the number of 1,4 double bonds does not pass through the origin is evidence that the double bonds in the vinyl side groups with a 1,2 structure present in the polymers give rise to an inverse structuralization process. When the oxygen concentration within the system is held constant, the kinetics of the process may be represented as follows. The rate at which the molecular chains break down, v_1, is proportional to the concentration C of 1,4 double bonds:

$$v_1 = k_1 \cdot C, \tag{1}$$

while v_2, the velocity of the structuralization processes, is proportional to the concentration $C_2 = (1-C)$ of 1,2 double bonds:

$$v_2 = k_2 (1-C). \tag{2}$$

Then V, the overall rate of destructive dissolution, is the algebraic sum of the two process rates:

$$V = v_1 - v_2 = -k_2 + (k_1 + k_2) C. \tag{3}$$

Fig. 3. Variation of the kinetic constants of the destructive dissolution of vulcanized rubbers with temperature: 1) sodium—butadiene rubber; 2) butadiene—styrene rubber.

As we have shown previously [1], the dissolution process takes place at a stationary rate in the surface layer, being governed by the initial concentration of double bonds. Hence, Equation (3) applies to the entire process, provided the surface of the vulcanized rubber being destroyed remains constant. The constants in Equation (3) depend upon the temperature, the oxygen partial pressure, and the absorption coefficient of the oxygen in the solvent. In the case of the dissolution in xylene at 120° and an oxygen pressure of 760 mm of pure vulcanized rubbers that contain tetramethylthiuram disulfide as an accelerator, Equation (3) may be written as follows:

$$V = -4.0 \cdot 10^{-6} + 1.2 \cdot 10^{-7} C. \tag{4}$$

where V is given in grams/cm^2·min, and C denotes the percentage of the total number of double bonds in the polymer that is represented by double bonds of 1,4 structure. This equation enables us to determine the percentages of 1,2 and 1,4 structures in the molecules of butadiene polymers experimentally.

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TABLE 2

Variation of the Rate of Destructive Dissolution of Vulcanized
Natural Rubber with the Composition of the Vulcanizing Group
Temperature 109°. Oxygen pressure approx. 760 mm Hg.

Composition of the vulcanizing group, parts by weight	Tensile strength, kg/cm^2	% elongation	Permanent elongation,%	Rate of dissolution, $\frac{g \cdot 10^5}{cm^2 \cdot min}$	Combined sulfur, %
Thiuram 0.2 Sulfur 2.0	176	840	6	3.0	1.48
Captax 0.8 Sulfur 2.75	221	850	12	3.87	1.47
Diphenylguanidine 1.0 Sulfur 3.5	190	880	10	2.31	1.35
Cymate 0.3 Sulfur	180	830	8	3.6	—
Vulcacite 0.25 Sulfur 2.0	180	950	8	3.4	—
Santocure 1.0 Sulfur 2.0	314	765	12	4.9	1.48

Fig. 4. Kinetic curves of the destructive dissolution of vulcanized natural rubber containing various vulcanization accelerators. Temp. 109°.
1) Captax; 2) Santocure; 3) Cymate; 4) Vulcacite; 5) tetramethylthiuram disulfide; 6) diphenylguanidine.

The polymer's structure likewise affects the apparent activation energy of the process of destructive dissolution. Determination of this variable required the prior determination of the temperature change in the absorption coefficient of oxygen in the solvent. With this objective, we worked out a method together with M. M.Rezinovsky [3] and found that the absorption coefficient of oxygen in xylene rises in the 23-100° interval in accordance with the following linear equation:

$$\frac{1}{A}^T = 150.5 + 0.395 \cdot t \qquad (5)$$

The kinetics of dissolution of the vulcanized rubber are given by the following equation:

$$\frac{dK_\alpha}{d\tau} = k[O] \cdot S, \qquad (6)$$

where [O] is the oxygen concentration in the solvent and S is the surface area of the vulcanized rubber.

If we insert in this equation the values of [O] calculated from Equation (5), the kinetic constants obtained for various temperatures approximately obey the Arrhenius equation (Figure 3). The apparent activation energy of destructive dissolution is 19 Cal/mole for a vulcanized natural rubber in the 87-107° range, 31.2 Cal/mole for a vulcanized sodium—butadiene rubber in the 116-128° range, and 27.12 Cal/mole for a vulcanized butadiene—styrene rubber in the 114-123° range.

The substantial increase in the activation energy from the natural rubber to the butadiene polymers is due precisely to the presence in the latter of double bonds in the vinyl side groups, which deflect the process into a steric structuralization.

2. Effect of the composition of the vulcanized rubber upon the kinetics of destructive dissolution. We investigated the effect of the vulcanizing group upon the kinetics of dissolution of vulcanized natural rubber. The composition and percentage of the other ingredients remained the same as in the original recipe (see above).

If the nature of the process kinetics is kept unchanged (Figure 4), a change in the composition of the vulcanizing group results in a change in the rate of destructive dissolution (Table 2), which is unrelated to the mechanical properties of the vulcanized films or the percentage of binding sulfur they contain. In view of the fact that the degree of vulcanization of the tested films was the same, the influence of the composition of the vulcanizing group upon the rate of destructive dissolution may be attributed to the chemical nature of the accelerator.

We have previously demonstrated [1] that mercaptans accelerate the dissolution of vulcanized natural rubber, whereas amines retard this process. It is also known [5] that tetramethylthiuram disulfide retards oxidation. As a matter of fact, rubbers that contain thiuram and diphenylguanidine do dissolve more slowly. Accelerators that possess a mercapto group in their molecule accelerate the dissolution of the rubber. This may be explained in

either of two ways: in some instances mercaptans accelerate the addition of oxygen; and they retard the poly-merization processes.

It should be borne in mind that in the procedure adopted, films of vulcanized rubber that had been ex-tracted in chloroform were subjected to the dissolution process, which eliminated the accelerators that had not reacted during vulcanization. Hence the accelerator or product of its interaction that affected the rate of destructive dissolution in our tests evidently existed in the vulcanized rubber in a combined state.
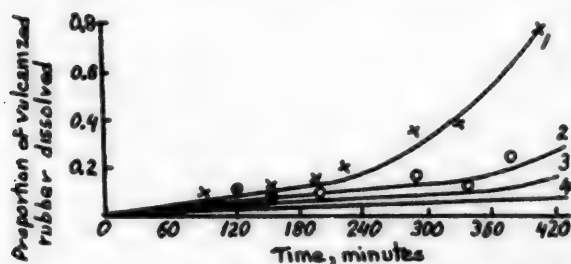
Fig. 5. Kinetic curves of the destructive dissolution of vul-canized sodium-butadiene rubber in various media. Temp. 110°. 1) Xylene; 2) ligroin; 3) toluene; 4) white spirit.

3. Effect of nature of solvent upon kinetics of destructive dissolution of vulcanized sodium-butadiene rubber. Fig. 5 gives the kinetic curves of the destructive dissolution of vulcan-ized sodium-butadiene rubber in various solvents: xylene, white spirit, cracking gasoline, ligroin, and toluene. The nature of the process kinetics remains unchanged, though the dissolution rate varies. Bearing in mind that the destructive dissolution is brought about by the action of oxy-gen, we might think that this phenomenon is due to the different solubility of oxygen in the sol-vents tested.

As has been pointed out, we designed a special device, described elsewhere [3], to deter-mine the solubility of oxygen in organic solvents. In contrast to apparatus of this type previously described, the preliminary degassing of the solvent was effected within the apparatus itself, the degassed solvent being drawn into the adsorption vessel by its own vapor pressure, which makes it possible to fabricate all connec-tions out of glass. As we see in Figure 6, the rate of destructive dissolution of the vulcanized rubbers is a linear function of the solubility of oxygen in the solvents tested. The sole exception to this rule is white spirit. The slowed dissolution of the vulcanized rubber in this solvent is apparently due to the fact that white spirit contains up to 10% of aromatic compounds, which may contain functional groups that retard the reaction with oxygen.

TABLE 3

Variation of the Rate of Destructive Dissolution of Vulcanized Sodium-Butadiene Rubber with the Solubility of Oxygen in the Solvent

Solvent	Temp. at which vulcanized rubber is destructively dissolved, °C	Rate of dissolution of the vulcanized rubber, grams/cm^2/min	Temp. at which the oxygen solubility was determined, °C	Oxygen solubility, ml per ml of solvent
Xylene	110	$6.3 \cdot 10^{-6}$	23.5	0.177
Ligroin	110	$4.6 \cdot 10^{-6}$	20	0.156
Toluene	110	$3.05 \cdot 10^{-6}$	20	0.129
White spirit	114	$1.72 \cdot 10^{-6}$	19	0.170

4. Effect of H_2O upon the kinetics of the destructive dissolution of vulcanized sodium-butadiene rubber. The procedure we utilized in studying the influence of water was the same, the sole difference being that oxygen saturated with water vapor was supplied to the device instead of anhydrous oxygen. The presence of water in the oxygen and in the solvent had no effect upon the nature of the kinetics of destructive dissolution of vulcan-ized natural and sodium-butadiene rubber (Fig. 7), though the rate of dissolution was slowed down in both cases.

We ran experiments to determine the effect of moisture upon the kinetics of oxidation of vulcanized rubbers in a solid film in order to ascertain the mechanism involved in the action of water during destructive dissolution. Oxidation was effected in a Nekrasov adsorption apparatus, the reaction vessels not containing any alkaline absorbents of the volatile oxidation products, of course. Water was introduced into the reaction vessel in the following manner. One or two drops of water were frozen in the vessel, after which the air was pumped out of the vessel,

and enough dry oxygen was supplied to allow for the expansion of the volume of oxygen and water as the temperature was raised to the experimental temperature. A parallel oxidation experiment was run with dry oxygen (again without any alkaline absorbents). The films of vulcanized rubber were prepared by applying a rubber paste of the desired composition and vulcanizing by the specified procedure.
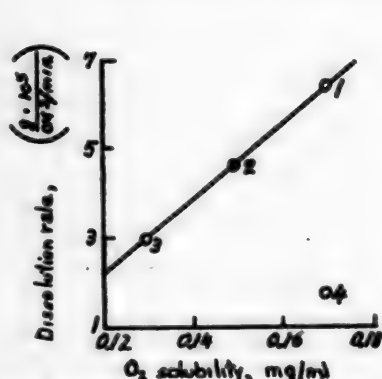

Fig. 6. Influence of the oxygen solubility in various solvents upon the rate of destructive dissolution of vulcanized sodium-butadiene rubber. 1) Xylene; 2) Ligroin; 3) Toluene; 4) White Spirit
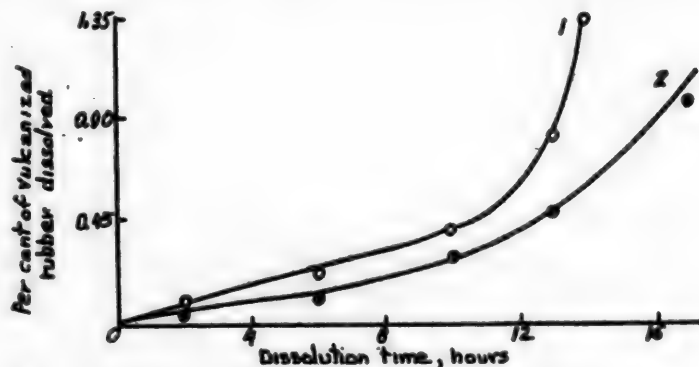
Fig. 7. Effect of water upon the kinetics of the destructive dissolution of vulcanized rubber. Temperature: 105°.
1) Anhydrous oxygen; 2) oxygen containing water vapor with a partial pressure of 22.4 mm Hg.

These experiments indicated that the presence of water in the oxygen, with its partial pressure corresponding to the temperature of the experiment, retards the addition of oxygen, at least during the period of vulcanized rubber oxidation that follows upon the induction period, apparently as the result of the water's decomposing the peroxide. Hence, the retarding action of water upon the dissolution of vulcanized rubber is related to the water's retardation of the addition of oxygen to the rubber (Figure 8).

5. Properties of destructively dissolved vulcanized sodium-butadiene rubber. The destructive dissolution of vulcanized sodium-butadiene rubber produces a faintly yellow opalescent solution. Methanol precipitates some 70% of the substance from solutions whose concentration is no lower than 5%, as a tacky mass that can be completely dissolved in all the ordinary rubber solvents after it is dried in vacuo at room temperature. Chemical analysis of destructively dissolved vulcanized rubber indicates that it contains free carboxyl groups (5.4 mg of carboxylic oxygen per gram of vulcanized rubber), and peroxide groups (1.2% of active oxygen). The total percentage of oxygen in the destructively dissolved vulcanized rubber (after precipitation with methanol) was about 4%).

The partial molecular weight of the destructively dissolved vulcanized rubber was determined by cryoscopy in benzene solutions whose concentration was at least 2%. It ranges from 3600 to 2400, the partial weight exhibiting a tendency to rise as the solution concentration drops. The osmotic partial molecular weight, extrapolated to zero concentration, was 16,000. There is no doubt that this weight represents the high-molecular fraction of the product, because of the permeability of the membrane for the low-molecular fraction.

The viscosity of solutions of the destructively dissolved vulcanized sodium-butadiene rubber (Fig. 9) is a linear function of the equation:

$$\eta sp = 24.0 \cdot v\text{-}C, \qquad (7)$$

where sp is the specific viscosity, v is the specific volume of the vulcanized rubber, and C is the concentration in grams per liter, throughout a wide range of concentrations. The numerical coefficient of this equation makes it possible to calculate the ratio of the axes of the ellipsoid of rotation, corresponding to the dimensions of the particles of the destructively dissolved vulcanized rubber, from Simha's table [6]. This ratio equals 15. According to Pasynsky [7], this ratio is 65 for the molecules of crude sodium-butadiene rubber.

The coefficient in Equation (7) is about 10 times as large as the numerical coefficient in the Einstein equation, which indicates that the effective volume of the particles of the destructively dissolved vulcanized rubber in the solution is 10 times as large as their volume in the solid state. We found that the volume of the initial vulcanized

rubber is increased by a ratio of 9.8:1 in xylene. Comparison of these figures indicates that the solution of the destructively dissolved vulcanized rubber contains massive particles that swell up in the solvent, constituting a sort of envelope of the steric structure of the vulcanized rubber.
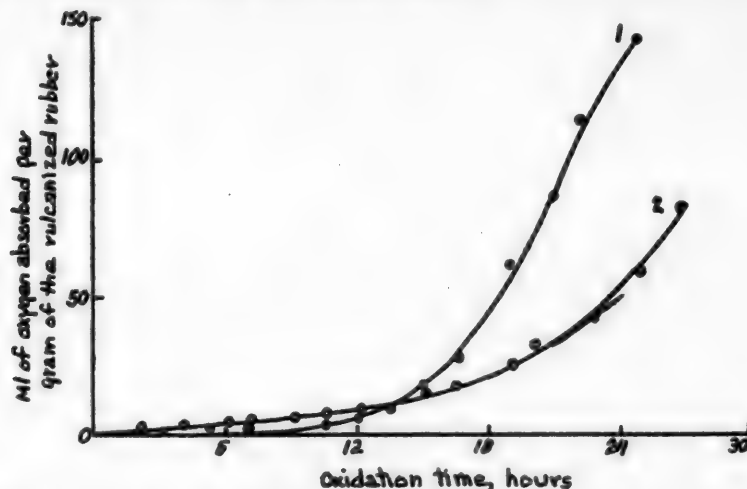

Fig 8. Effect of moisture upon the kinetics of the absorption of oxygen by vulcanized natural rubber. Temperature: 108°. 1) Dry oxygen; 2) moist oxygen.

Thus the solution of destructively dissolved vulcanized rubber constitutes a new type of lyophilic colloidal system. Some of the characteristics (form, presence of a surface of separation) of the system described class it as a lyophobic colloid, thus differing from the solutions of ordinary high-molecular compounds. The system differs from typical lyophobic colloids in so far as the conditions governing its stabilization are concerned, which is determined by the ability of its particles to swell up in a solvent. What is more, the primary particles of the disperse phase of a solution of a destructively dissolved vulcanized rubber constitute a system of atoms linked by principal valency forces, wherein they differ from the particles in the disperse phase of lyophobic colloids.
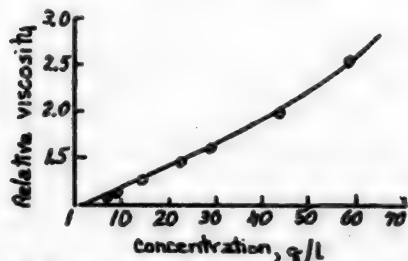
Fig. 9. Variation of the viscosity of solutions of destructively dissolved vulcanized sodium-butadiene rubber with their concentration.

SUMMARY

1. Vulcanized synthetic rubbers dissolve completely when heated in hydrocarbon media that contain molecular oxygen. The kinetics of the destructive dissolution of vulcanized synthetic rubbers are governed by the laws established for the destructive dissolution of vulcanized natural rubber.

2. The rate of destructive dissolution of vulcanized rubbers depends upon the molecular structure of the rubbers. The destructive dissolution rates of vulcanized rubbers increase progressively according to the following series: butyl rubber < sodium-butadiene rubber < butadiene-styrene rubber < chloroprene rubber < natural rubber. The apparent activation energy is 19 Cal/mole for natural rubber, 31.2 Cal/mole for sodium-butadiene rubber, and 27.1 Cal/mole for butadiene-styrene rubber.

3. The rate of destructive dissolution of vulcanized butadiene rubbers is a linear function of the percentage of 1,4 structures in the rubber molecule.

4. The mechanical properties of the vulcanized rubbers have no perceptible effect upon the rate of their destructive dissolution. The type of accelerator employed is of basic importance, their influence corresponding to their effect upon the rate at which oxygen is added.

5. The presence of water retards the dissolution of vulcanized natural and sodium-butadiene rubber, because the H_2O retards the process of oxygen addition.

6. The rate of destructive dissolution of vulcanized rubbers in various solvents is a linear function of the absorption coefficient of oxygen in these solvents.

7. The viscosity of solutions of destructively dissolved vulcanized sodium-butadiene rubber is a linear function of concentration up to 5%.

8. The mean partial molecular weight, determined cryoscopically, ranges from 2400 to 3600 for vulcanized sodium-butadiene rubber, the osmotic value being 16,000. The axial ratio of the particles is 1:15.

9. It is asserted that solutions of destructively dissolved vulcanized rubber represent a special type of colloidal solutions.

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NEW TYPES OF TERPENE TRANSFORMATIONS

VIII. SYNTHESIS OF TERPENYLACETOACETIC AND TERPENYLMALONIC ESTERS AND OF THEIR CLEAVAGE PRODUCTS

D. Tishchenko and V. Foliadov

In our Report VII [1] we set forth general considerations regarding the anion-exchange reactions of allylic chloroterpenes and described methods of synthesizing ethers and esters of $C_{19}H_{15}OR$ terpenols. We showed that a solvent yielding the same anion as the reagent (say, acetic acid and potassium acetate) must be used if a high yield of the desired product is to be obtained in an anion-exchange reaction.

Inasmuch as allylic chloroterpenes have been unknown prior to this, the corresponding acetoacetic and malonic esters have been likewise unknown. We fixed upon the thermally stable 6-chlorodipentene [2] for our research into the feasibility of synthesizing these esters. In accordance with the foregoing, the synthesis of these esters should be carried out in a large excess of malonic or acetoacetic esters as solvents of sodium-substituted esters. But we did not have large quantities at our disposal, so that we synthesized the sodium-substituted esters in toluene at 100°, using calculated quantities of the ester and of sodium and then adding 6-chlorodipentene. It was impossible to utilize absolute alcohol as the solvent, for then the principal reaction product would be 6-ethoxydipentene [1]. The reaction of 6-chlorodipentene with the sodium derivatives of the specified esters in toluene is much slower than with potassium acetate in acetic acid. The reason for this is evidently that toluene is not a good enough ionizing solvent for either the chloroterpene or the sodium-substituted ester, owing to its low dielectric constant, wherein it differs from acetic acid. As a result, the rate of ionization of the chloroterpene, which governs the overall conversion rate, is low, with the consequences that follow therefrom.

The conversion we are interested in are far from finished after 16-24 hours of heating; being only 30-70% complete, though there are no side reactions: the unreacted portion of the chloroterpene being recovered unchanged, and the balance sheet of the initial and synthesized substances tallying.

6-Chlorodipentene was condensed with the sodium derivatives of acetoacetic, methylacetoacetic, and malonic esters. The resulting 6-dipentenyl esters were viscous, high-boiling liquids. The 6-dipentenylacetoacetic ester was subjected to ketonic cleavage, the 6-dipentenylmethylacetoacetic ester being subjected to both ketonic and acidic cleavage, thus yielding hitherto unknown ketones (6-acetonyldipentene and 6-isobutanonyl-dipentene) and the unknown methyl-6-dipentenylacetic acid.

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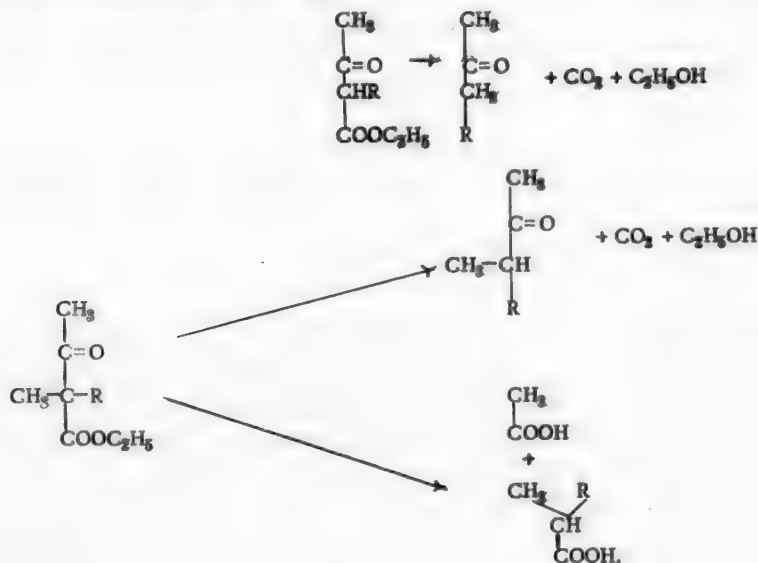
where R = 6-dipentenyl.

The dipentenylmalonic ester was saponified to the corresponding dipentenylmalonic acid, from which carbon dioxide was split out to produce dipentenylacetic acid, RCH_2COOH.

The two new ketones are mobile liquids with very pleasant fragrances. Their analyses indicated that they were somewhat impure. Their semicarbazones were secured in an analytically pure state. We were unable to crystallize any of the acids mentioned.

As the cited findings indicate, it is possible to synthesize terpenylacetoacetic and terpenylmalonic esters readily from thermally stable chloroterpenes. This is further [1] confirmation of the feasibility of synthesizing unknown or difficultly accessible terpene derivatives with the same degree of unsaturation and the same carbon skeleton as the original terpene, which we had postulated previously.

EXPERIMENTAL

Synthesis of 6-dipentenylacetoacetic ester. The 6-chlorodipentene had a b.p. of 68° (2 mm); d_4^{20} 0.9926; n_D^{20} 1.4979; the percentage of saponifiable chlorine was found to be 19.5, 19.8, the calculated value being 20.7.

100 ml of anhydrous toluene and 2.7 g of sodium were placed in a round-bottomed flask fitted with a stirrer and a reflux condenser. The flask was heated until the sodium melted, after which the stirrer was stopped and 15.3 g of ethyl acetoacetate was added drop by drop. After 6 hours of stirring at 100° (bath temperature), all the sodium was converted into a gelatinous precipitate of the sodiumacetoacetic ester. The mixture was stirred and heated while 20 g of the chloroterpene was added. Eight hours later, while the precipitate was fully stirred up with the stirrer, a sample was taken with a pipet (the total volume being known) and the NaCl content of the sample was determined. The reaction was 58% complete. Heating and stirring were continued for another 8 hours, after which the reaction was 66.5% complete. The precipitate was suction filtered, washed with toluene, and dissolved in water, the solution being extracted with ether. The percentage of Cl was determined in the aqueous solution; the reaction was 69.6% complete. The coarse method (see above) yielded 66.5%, which indicated that it could be employed to check the progress of the reaction. The ether and the toluene were eliminated from the filtrates, the residue weighing 28.5 g; it was distilled at 0.2 mm, yielding: Fraction 1 (to 55°), 3.85 g; and Fraction 2 (55°), 2.95 g. Fraction 1 colored ferric chloride crimson and contained 9.2% chlorine, i.e., it was a mixture of approximately equal parts of the acetoacetic ester and the chlorodipentene; Fraction 2 contained 20.6% of chlorine (chlorodipentene). The residue was fractionated molecularly at 0.001 mm, yielding: Fraction 1 (bath temperature up to 80°), 1.70 g; Fraction 2 (bath temperature 80-85°), 15.55 g; and a residue of 2.65 g, which did not distil on a boiling water bath.

Fraction 1 contained 12.8% of chlorine and colored $FeCl_3$ crimson, i.e., it contained a chloride and the sought-for ketone ester; Fraction 2 colored $FeCl_3$ red and had the following constants:

d_4^{20} 1.0144; n_D^{20} 1.4891; MR_D 75.18; calculated for the keto form 74.62.
Found %: OC_2H_5 17.8, 17.5. $C_{18}H_{24}O_3$. Calculated %: OC_2H_5 17.1.

Ketonic cleavage of the ketone ester. 16 g of Fractions 1 and 2 was steam-distilled with 140 ml of 7% potassium hydroxide. The distillate was extracted with ether, the ether driven off from the extract, and the residue (10.8 g) fractionated into a small column at 1 mm, yielding: Fraction 1 (53-85°), 1.10 g; Fraction 2 (85-87°), 6.8 g; Fraction 3 (87-120-122° 2.2 g; and 0.5 g of residue.

Fraction 1 contained chlorine, being a mixture of a chloride and the ketone; the constants of Fraction 3 were d_4^{20} 1.014; n_D^{20} 1.4924; % OC_2H_5 17.4; and it represented the initial ketone ester; Fraction 2 possessed a highly fragrant, slightly sharp odor.

d_4^{20} 0.9353; n_D^{20} 1.4880; MR_D 59.19; $C_{10}H_{15}CH_2COCH_3 \cdot F_2$. Calculated 59.11. Found %: C 78.6, 78.7; H 11.1, 11.2. $C_{13}H_{20}O$. Calculated %: C 81.2; H 10.6.

Semicarbazone of 6-acetonyldipentene. 0.7 g of semicarbazide hydrochloride and 0.65 g of potassium acetate were separately dissolved in alcohol and then poured together, the KCl being suction filtered, and 1.2 g of the ketone being added to the filtrate. The solution was heated to 60°, and water was added a drop at a time until the resulting turbidity disappeared with difficulty. The flask was stoppered with cotton. Two hours later crystals of the semicarbazone with a m.p. of 117-118° settled out nearly quantitatively. The m.p. was constant at 129.5-130° after the fourth recrystallization from alcohol.

Found %: N 16.5, 17.2. $C_{14}H_{23}ON_3$. Calculated %: N 16.9.

Synthesis of 6-dipentenylmethylacetoacetic ester. This was effected under the conditions set forth above. 6.5 g of sodium; 250 ml of toluene; 44 g of methylacetoacetic ester; and 48.5 g of 6-chlorodipentene; 18 hours of heating on a water bath. The reaction product was diluted with an equal volume of water and neutralized, while stirred, with normal nitric acid; the toluene and aqueous layers were separated; and the percentage of Cl in the latter layer was determined. The reaction was 63.4% complete. The toluene was driven off from the toluene layer in a water-jet vacuum with an adapter, the residue weighing 70 g. Molecular fractionation of the residue at 0.001 mm and a bath temperature not in excess of 100° yielded 52.8 g of distillate, the residue totaling 9 g, and the losses 8.2 g, as indicated by the toluene balance sheet. The distillate contained 6.85 g of chlorine, equivalent to 17.4 g of the chloride. If the reaction had been 63.4% complete, we should have gotten 17.8 g of the chloride. 52.35 g of the distillate was fractionated at 1 mm into a column with an efficiency of 3-4 theoretical trays and a reflux ratio of 8-10. Fraction 1 (43-120°) weighed 13.65 g; Fraction 2 (120-135°), 5.05 g; Fraction 3 (135-137°), 30.75 g; the residue was 2.05 g; and the losses 0.85 g. Fraction 3 contained no chlorine.

d_4^{20} 1.017; n_D^{20} 1.4889; MR_D 78.83. $CH_3COC(C_{10}H_{15})(CH_3)COOC_2H_5 \cdot \Gamma_2$. Calculated 78.81. Found %: OC_2H_5 16.5. $C_{17}H_{28}O_3$. Calculated %: OC_2H_5 16.2.

Ketonic cleavage of the ester. 19.75 g of the ester and 200 ml of 7% potassium hydroxide were distilled with steam. The oil was extracted from the distillate with ether; the ether being driven off and leaving a residue of 17.4 g. The residue was fractionated at 1.6 mm into a small column with a reflux ratio of 8-10: Fraction 1 (85-102°), 0.5 g; Fraction 2 (102-109°), 3.15 g; Fraction 3 (109-130°), 3.55 g; Fraction 4 (130-138°), 7.15 g; and a residue of 1.05 g. Fraction 4 was the initial ketone ester (d_4^{20} 1.026; n_D^{20} 1.4901). Fractions 2 and 3 were refractionated at 1.25 mm: Fraction 1 (96-98°), 5.2 g; Fraction 2 (98-108°), 0.9 g; and a residue of 0.5 g. The constants of Fraction 1 were: d_4^{20} 0.9378; n_D^{20} 1.4834; MR_D 62.83. $CH_3COCH(CH_3)C_{10}H_{15} \cdot \Gamma_2$. Calculated 63.37. The ketone is a liquid with a pleasant fragrance that is somewhat different from that of the preceding one. Its negative exaltation is evidence of its incomplete purity.

Semicarbazone of isobutanonyl-6-dipentene. This was prepared by the method described above. The crystals settled out 24 hours later, rather than after 2 hours, which conforms with the greater degree of branching of this ketone. A constant m.p. of 127-127.5° was attained after three recrystallizations from methanol. Found %: N 16.2, 16.3. $C_{15}H_{25}ON_3$. Calculated %: N 16.0.

Synthesis of the 6-dipentenylmalonic ester. 300 ml of toluene and 2.7 g of sodium. The mixture was heated to 100° and stirred while 29 g of malonic ester was added in the course of 2.5 hours, followed by 20.5 g of the chlorodipentene. Heating lasted 2.5 hours. After cooling, the reaction product was neutralized with dilute nitric acid (1:5). The toluene layer was removed, and the percentage of chlorine in the aqueous layer determined, indicating that the reaction was 35.6% complete. The toluene was driven off from the toluene layer at 12 mm into a column, the residue weighing 44 g. The 52-60° overhead fraction (24.5 g, containing 7.7% of chlorine) was distilled at 0.1 mm, the residue weighing 16.2 g; of the latter 14.3 g was fractionated at 0.01 mm, yielding: Fraction 1 (53-112°), 1.1 g; Fraction 2 (112-113°), 8.7 g; and Fraction 3 (113-119°), 2.5 g.

Fraction 2: d_4^{20} 1.031; n_D^{20} 1.4755; MR_D 80.82. $C_{10}H_{15}CH(COOC_2H_5)_2$. Calculated 80.87. Found %: OC_2H_5 29.5, 29.1. $C_{17}H_{28}O_4$. Calculated %: OC_2H_5 30.6.

Fraction 3: d_4^{20} 1.025; n_D^{20} 1.4769; MR_D 81.7. % OC_2H_5 29.9. The distillation residue (1.1 g) contains 26.9% of OC_2H_5. The yield of the dipentenylmalonic ester is equivalent to mineralized chlorine.

Saponifying the ester. 7.45 grams of the ester was heated to 100° for 3 hours with 4 g of KOH and 3 ml of water. The alcohol and the unsaponified ester were blown off with steam, the residue being extracted with ether, and the alkaline solution acidulated with Congo red and extracted with ether. The ether was driven off from the extract, the residue, a viscous liquid, weighing 5.9 g. The gram equivalent was found to be 133, the computed value for dipentenylmalonic acid being 119; an acid ester is evidently present as an impurity. The ester is freely soluble in all solvents, with the exception of gasoline; when its solutions are evaporated, a thick oil settles out.

Decomposing dipentenylmalonic acid. 4.9 grams of the acid was heated on a metallic bath until no more carbon dioxide was given off, evolution beginning at 110° and ceasing at 190°. The residue weighed 3.70 g, though it should weigh 3.55 g. The gram equivalent was found to be 228, the calculated value for dipentenylacetic acid ($C_{12}H_{18}O_2$) being 194. The acid contains neutral impurities. The silver salt, prepared in the usual manner, yielded nearly the calculated percentage of silver upon analysis (35.5, 35.6%; calculated 35.7%).

Synthesis of methyl-6-dipentenylacetic acid. 6.7 grams of methyldipentenylacetoacetic ester (see above) was heated to 100° with 17 g of an 82% solution of KOH for 3 hours 45 minutes. Steam was blown through the solution to remove the neutral substances, the solution being extracted with ether after cooling for the same purpose, and then acidulated with Congo red. The oil was extracted with ether, and the ether driven off, the residue weighing 3.6 g. The gram equivalent was found to be 216, the calculated value being 208. The acid was purified by molecular distillation at 0.001 mm and a bath temperature of 80-90°, which reduced the gram equivalent to 210. The acid did not crystallize.

Found %: C 74.4; H 9.9. $C_{13}H_{20}O_2$. Calculated %: C 74.9; H 9.7.

The silver salt was prepared in the usual manner.

Found %: C 49.4; H 6.2; Ag 34.1. $C_{13}H_{19}O_2Ag$. Calculated %: C 49.5; H 6.1; Ag 34.2.

SUMMARY

1. 6-Chlorodipentene has been used to show that terpenylacetoacetic and terpenylmalonic esters can be synthesized.

2. Ketones and acids of the homoterpene series can be prepared from these esters in the usual manner.

3. These facts support our previous postulate that diversified new syntheses can be carried out using the chloroterpenes, yielding hitherto unknown or difficultly accessible derivatives of terpenes in which neither the carbon skeleton nor the degree of unsaturation of the terpene is changed.

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THE FORMATION OF PHENOLS IN THE CATALYTIC CONDENSATION OF ACETONE

WITH ACETIC ANHYDRIDE. III

B. N. Dolgov, T. V. Nizovkina, and L. V. Mozzhukhina

When ethyl alcohol is condensed with acetone over an $Al_2O_3 - Fe_2O_3$ catalyst at 400-410°, condensate is formed that contains 5% of phenols, the bulk of which consists of 3,5-dimethylphenol [1]. On the basis of the existing research papers and analytic findings the suggestion was put forward that this is a complex process, the first stage of which is the dehydrogenation of ethyl alcohol to acetaldehyde, which then condenses with the acetone, forming the final phenol. In our study of the behavior of several alcohol-ketone systems we secured the corresponding phenols that were predicted by the proposed mechanism; to a certain degree this constitutes a proof that the latter is correct. We also undertook the present research on the acetaldehyde—acetone system to prove that the formation of phenols from alcohols and ketones involves a preliminary stage in which the alcohols are dehydrogenated to aldehydes.

The $Al_2O_3-Fe_2O_3$ catalyst was prepared as described in our preceding report [2], its activity being tested by producing phenols from a mixture of ethyl alcohol and acetone. The phenol yield was 6%. A mixture of acetaldehyde and acetone was passed over this catalyst under varying conditions and the percentage of phenols in the condensate was determined. As in our previous researches, the optimum temperature was found to be 400-410°, as indicated by the following figures:

Temperature	380-390°	390-400°	400-410°	410-420°
Per cent of phenols	4.45	5.42	9.4	7.47

The optimum volumetric rate was found to be 31-33. The activity of the catalyst dropped appreciably after 2 hours of operation, but was restored in full after oxygen had been blown through at 450-500°. The deactivation of the catalyst is caused by the deposition of tarry films on the contact surface. The gain in weight totaled 2.56% of the catalyst's weight after 2 hours of operation, or 9.5% of the mixture throughout. The mixture of acetaldehyde and acetone yields nearly twice as much of the phenols as the mixture of ethyl alcohol and acetone (9.5 and 5.1%, respectively).

The condensates constituted a two-layer liquid, consisting of an oily and an aqueous layer. The phenols were extracted by processing the condensate twice with 10% NaOH, after which the alkaline solution was separated from the oil and acidulated with 10% H_2SO_4. Analyses of the condensates indicated that their mean composition is as follows: 9.5% phenols, 33.2% neutral oil, 39.4% unreacted mixture, and 15.3% water. The phenols are probably formed only via the joint condensation of acetaldehyde and acetone, inasmuch as neither the aldehyde nor the acetone by itself yields phenols, as has been proved by special tests. The highest phenol yield is attained with an equimolecular mixture of the reagents (1:1).

Analysis of the phenolic oil indicated that its principal constituent was 3,5-dimethylphenol. We also found a slight percentage of ethylphenol. The production of the former bears out our hypothesis that the condensation involves the intermediate formation of β-diketones as follows:

$$CH_3COCH_3 + HOC - CH_3 \rightarrow CH_3COCH_2CHOHCH_3$$
$$CH_3COCH_2CHOHCH_3 \rightarrow CH_3COCH_2COCH_3 + 2H$$

3,5-Dimethylphenol
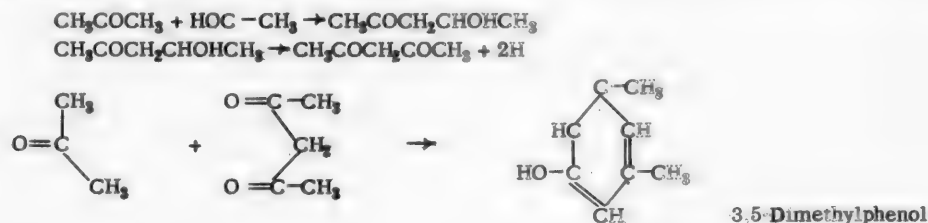
The higher fractions of the phenolic oil constituted complex mixtures of high-molecular phenols; we were unable to separate them or to identify the individual phenols by existing methods.

The neutral part of the oil, which was insoluble in alkali, distilled continuously in the 50-250° range. The residue was a black resin (30% of the oil). The composition of the resin was determined by destructive distillation [3]. Analysis of the decomposition products indicated that the resin contains condensed phenols and aldehyde, i.e., its composition is close to that of Bakelite. Treating the phenols obtained by destructively distilling the resin with chloroacetic acid in the presence of NaOH yielded a mixture of aryl glycolic acids with a broad melting point (in the neighborhood of 11°). These results indicate that the condensation of aldehyde with acetone goes much deeper than we had supposed. The formation of individual phenols from the acetaldehyde and the acetone is paralleled by a more thoroughgoing condensation of the aldehyde with the synthesized phenols, yielding phenolic-aldehydic resins. Thus, the phenolic oil consists of only that part of the total phenols secured from the aldehyde and the acetone which did not enter into further condensation. A very rough calculation indicates that 25-30% of phenols are produced per single pass.

The fraction with a b.p. of 50-250° was fractionated into a Todd column, yielding a series of fractions, the investigation of these fractions and the isolation of individual products from them being greatly hampered by the fact that secondary dehydration and polymerization reactions in the flask accompanied the fractionations. We found that all the fractions contained ketones, though only methyl ethyl ketone could be isolated and identified. Unreacted acetaldehyde and acetone were recovered from the neutral aqueous layer.

EXPERIMENTAL

The experiments on the condensation of acetaldehyde with acetone were performed in the usual catalytic apparatus, using a tubular electric furnace (24 cm platform). The temperature was measured with an iron-constantan thermocouple placed in the catalyst zone. The $Al_2O_3-Fe_2O_3$ catalyst was prepared by introducing the calculated quantity of Al_2O_3, with stirring, into ferric nitrate that had been fused in its own water of crystallization. The resultant mixture was stirred to a thick paste with a 5% solution of starch and dried for half an hour at 70-80°, after which it was formed into coils (2 mm), which were dried out at 100°. After the catalyst had been placed in the reaction tube it was exposed to a strong current of air at 450-500° until no more nitrogen oxides were evolved. In every run, a mixture of acetaldehyde and acetone was passed over 100 ml of catalyst at a volumetric rate of 31-33. The optimum reaction temperature was 400-410°. Ninety runs were made to accumulate a large enough amount of the condensate.

The resulting two-layer condensate was first distilled to drive off the fraction up to 60°, which contained most of the unreacted aldehyde and acetone, after which the contents of the reaction flask separated into two layers: the upper one a dark oil and the lower one a light-yellow aqueous layer with a slightly acid reaction. The aqueous layer distilled at 100°, leaving practically no residue.   It   was nearly pure water. The oily layer contained no acids. Its phenols were extracted by agitating it twice with 10% NaOH. The phenolate solution was washed with ether to free it of the partially extracted drops of neutral oil and then decomposed with 10% H_2SO_4. The resulting phenols were extracted with ether, dried, and weighed after the ether had been driven off. The neutral part of the oil was given the same treatment after the phenols had been eliminated. A flow-sheet test, with analysis of the condensate, yielded the following results:

Mixture throughput	12.5 g
Condensate secured	11.0 g
Volume of gas evolved	660 ml
Weight of carbon on the catalyst	1.2 g
Weight of aldehyde in trap	0.01 g

Analysis of the phenolic oil. The phenolic oil was fractionated, yielding the following narrow fractions: 1) 177-192°, 0.2 g; 2) 192-196° , 1.3 g; 3) 198-202°, 1.5 g; 4) 203-210°, 2.8 g; 5) 211-214°, 2.8 g; 6) 215-220°, 2.9 g; and 7) 221-226°, 2.1 g. The residue, with a b.p. about 226° (27%) constituted a complex mixture of higher phenols and was not analyzed further. All the fractions were analyzed by the Holzmann and Pilat method of preparing aryl glycol acids [4] to determine the percentages of the individual phenols they contained; part of the tested phenolic fraction was mixed with an equal quantity (by weight) of NaOH, ground to fine powder, a few drops of water were added, and the mixture was stirred until a phenolate was formed, after which it was vigorously stirred while an equal quantity by weight of monochloroacetic acid was

added. The reaction was carried out in the cold, giving rise to foaming and the liberation of heat. The resultant melt was dissolved in hot water, the aryl glycolic acids being extracted by adding HCl and extracting with ether. The ether extract was treated with a soda solution to eliminate the unreacted phenol. Acidulating the soda extract precipitated an aryl glycolic acid, which was recrystallized from water. In this manner Fraction 2, with a b.p. of 192-196°, yielded an aryl glycolic acid with an m.p. of 80.5-81.5°, which was 3,5-dimethylphenoxyacetic acid (m.p. of 81°, according to the literature). The same acid was secured from the 198-202° and 211-214° fractions. The mixed melting points of these acids with one another exhibited no depression, which was evidence of their identity. The molecular weight was determined by titration with alkali.

Found %: C 66.34, 66.53; H 6.83, 6.92; M 179, 179.4. $C_{10}H_{12}O_3$. Calculated %: C 66.66; H 6.7; M 180.

The 215-230° fraction yielded an aryl glycolic acid with a broad melting point, which constituted a mixture of two acids, which were separated by fractional crystallization from water. One of them was 3,5-dimethylphenoxyacetic acid (m.p. 79-80.5) while the other was p-ethylphenoxyacetic acid (m.p. 96-97°; the m.p. given in the literature is 96-97°). The molecular weight of the latter was determined as 177 (the calculated value being 179). The 203-210° and 221-226° fractions yielded a complex mixture of aryl glycolic acids, from which we were unable to isolate individual acids. Analogous results were obtained when twice and three times the quantities of alkali and monochloroacetic acids were employed.

The neutral part of the oil, separated from the phenols, was driven off at 50-250°, leaving a tacky black resin that solidified upon cooling (30% of the initial oil) within the distilling flask. The distillation product was carefully fractionated into a Todd flask, yielding 13 fractions, which were analyzed individually. All the fractions contained ketones, the fractions that boiled above 90° constituting complicated mixtures, from which no individual component could be isolated. The lower fractions contained 89-96% of unreacted acetone. The latter was determined as a p-nitrophenylhydrazone with an m.p. of 146-147°. The 78-82° fraction was found to contain methyl ethyl ketone, as was proved by securing the p-nitrophenylhydrazone with an m.p. of 126-127°. The latter exhibited no depression of the melting point when mixed with the p-nitrophenylhydrazone secured from known methyl ethyl ketone. The semicarbazone of methyl ethyl ketone, which had an m.p. of 134-136° (the literature gives 136°), was secured and tested in a similar manner.

Found %: N 32.88, 32.74; $C_5H_{11}N_3O$. Calculated %: N 32.53.

The resin left within the flask after the neutral oil had been driven off up to 250° was subjected to dry distillation, the resulting liquid products being analyzed qualitatively. They exhibited a positive silver mirror reaction (acetaldehyde). The phenolic constituents were determined by producing a mixture of aryl glycolic acids, which we were unable to separate into the individual components.

SUMMARY

1. Condensing acetaldehyde with acetone over an Al_2O_3—Fe_2O_3 catalyst at 400-410° yields a condensate that contains 9.5% of phenols, of which 3,5-dimethylphenol and ethylphenol were identified.

2. The neutral oil left behind after the phenols had been isolated consists of acetone, methyl ethyl ketone, and a complex mixture of higher ketones.

3. After the neutral oil has been driven off up to 250°, there is left behind in a flask 30% of a black resin of the Bakelite type, containing aldehyde and phenols. A preliminary estimate is that 25-30% of phenols are produced per single pass from acetaldehyde and acetone.

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** See Consultants Bureau translation, p. 697.

SYNTHESIS OF 1,1,1-TRICHLORO-p.p'-DIAMINODIPHENYLETHANE AND ITS DERIVATIVES

I. Kh. Feldman and A. I. Zitser

In 1944 the hypothesis was put forward in the literature [1] that the amino analog of the well-known insecticide dichlorodiphenyltrichloroethane (DDT)—1,1.1-trichloro-p,p'-diaminodiphenylethane (III)—might be active against tuberculosis bacilli. Attempts were then made to synthesize this compound, but, to judge from the published findings, only Kirkwood and Phillips [2] succeeded in isolating the diamine (III) in the individual state. The same authors state that the diamine (III) synthesized by them and its unsaturated compound 1,1-dichloro-p,p'-diaminodiphenylethylene (V) retard the growth of tuberculosis bacilli in vitro in a 1:100,000 dilution. They also reported that the compound (III) exhibited a perceptible effect upon experimental tuberculosis in guinea pigs.

We repeated the synthesis of these compounds as follows:
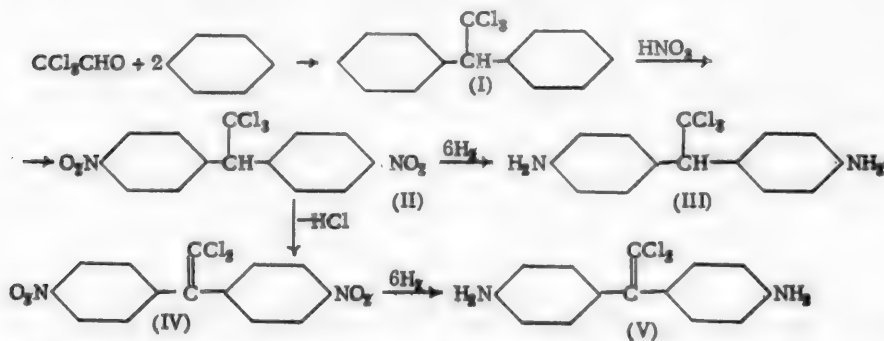
in order to make a study of the chemotherapeutic properties of the above-mentioned compounds.

Condensing chloral with benzene, as indicated by Baeyer [3], results in a nearly quantitative yield of 1,1,1-trichloro-2,2-diphenylethane [1], whose m.p. was 62-64° after crystallization from alcohol. When we repeated the nitration reaction under exactly the same conditions as those described by Kirkwood and Phillips, viz. nitrating with nitric acid ($d = 1.5$) at 30° and stirring for 4 hours at room temperature, we did not secure a 63% yield of the recrystallized product with an m.p. of 166-167°, as stated by the authors. We obtained only a 25-26% yield of the nitro compound (II) with the stated melting point after two or three recrystallizations from glacial acetic acid. Nor did the carrying out of the reaction as specified by Haskelberg and Lavie [4], who performed nitration at -30°, increase the yield of the pure product.

We have worked out a nitration method that furnishes a 40-43% yield of the pure recrystallized nitro compound with a m.p. of 166-167°. Nitration is carried out in chloroform by a mixture of nitric acid ($d = 1.5$) or sulfuric acid ($d = 1.84$) and solid potassium nitrate.

Reducing the nitro compound (II) with Raney's nickel in glacial acetic acid at a pressure of 4 atmospheres yields an amino compound, the m.p. of which was 149-150° after purification. The substance is darkened when it is recrystallized from alcohol, its melting point dropping. The yield of the recrystallized product is very low. We secured a pure product, with a fully satisfactory analysis, by double reprecipitation of the amine from its hydrochloride. The amine thus purified has been kept for several months in a closed container without suffering any change in its melting point or its chlorine content. It is worthy of note that reduction was slow when it was carried out in acetic acid that contained a slight trace of acetic anhydride, and that, instead of the amine (III) we obtained nothing but its acetyl derivative—1,1,1-trichloro-bis-(p-acetylaminophenyl)-ethane, with an m.p. of 258-259°, which was identical with the compound produced by

acetylating the amine (III) with acetic anhydride in pyridine.

Eliminating the HCl from the nitro compound (II) by the use of alcoholic alkali results in the synthesis of 1,1-dichloro-bis-(p-nitrophenyl)-ethylene (IV), with an m.p. of 172-173°.

The reduction of (IV) to an amine is effected quite smoothly by using Raney's nickel in glacial acetic acid at normal pressure. The melting point of the amine is 144-145°. Here, too, when we use acetic acid that contains some acetic anhydride, we get nothing but 1,1-dichloro-bis-(p-acetylaminophenyl)-ethylene, with an m.p. of 294-296°, identical with that obtained when we acetylated the unsaturated amine.

We also reduced the nitro compounds (II) and (IV) with stannous chloride and hydrochloric acid. The yield of the amine (III), with an m.p. of 149-150°, rose to 90% of the theoretical under these conditions. The amines synthesized by catalytic reduction and by reduction with stannous chloride were completely identical. When we reduced the nitro compound (IV) by this method, we secured the amine (V) with an m.p. of 144-145°, its yield being 90% of the theoretical, which was identical with the product obtained catalytically.

Tests of the action of Compounds (III) and (V) against tuberculosis bacilli, made in the Division of Chemotherapy of our institute by O.A. Makeeva, did not confirm the findings of Kirkwood and Phillips, however. These substances produced only negligible retardation of the growth of tuberculosis bacilli in vitro. This circumstance forced us to repeat the proof of the structure of the compounds we had synthesized as follows:

(m.p. 118-189°)   (m.p. 240-241°)

(m.p. 236-237°)
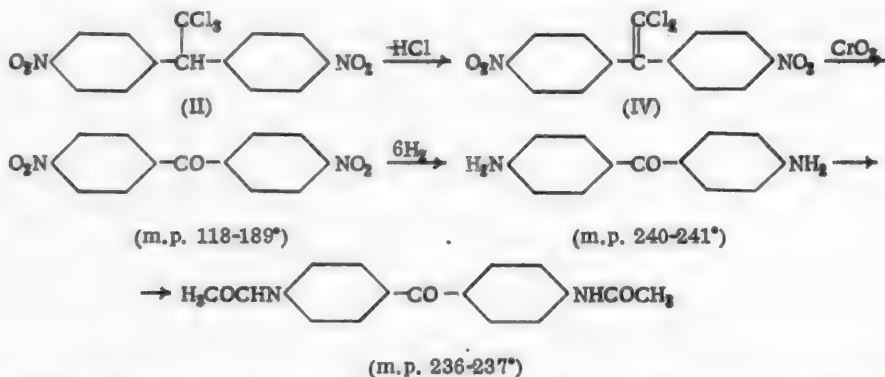
It was thus established that the compound (II) has the structure of p,p'-dinitrodiphenyldichloroethylene.

To prove that no rearrangements such as are known in this series take place during reduction, we performed the following series of transformations:


(III)

(m.p. 294-296°)

(m.p. 236-237°)
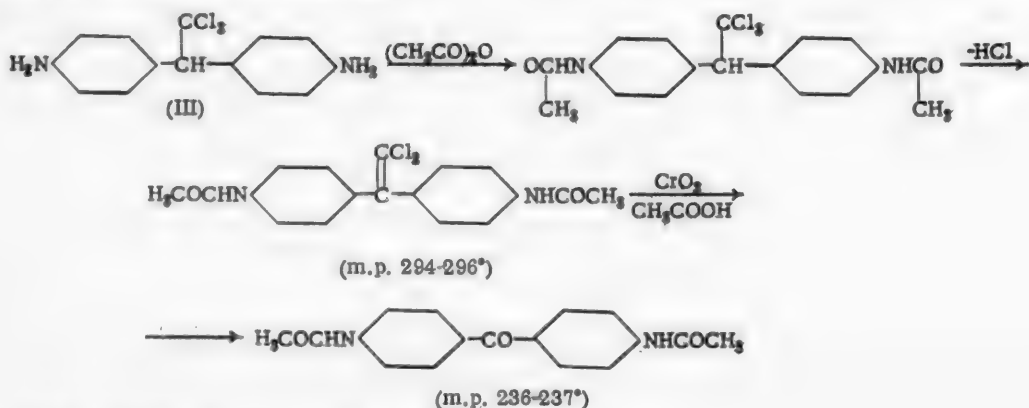
All these melting points agree with the figures given in the literature.

It may therefore be taken as proven that the compound (II) we have synthesized is 1,1,1-trichloro-2,2-bis-(p-aminophenyl)-ethane.

We then obtained the products of the condensation of the amines (III) and **(V)** with **aldehydes.** In these condensations we used salicylaldehyde, cotarnine, phthalaldehydic acid, and opianic acid.

Ortho aldehydic acids can react with amines in the aldehydic form or in the tautomeric phthalidic form. Depending upon the form in which these acids react with the amines, the compounds synthesized by us will have either the azomethine structure (VI) or the phthalide structure (VII):

(VI)

(VII)
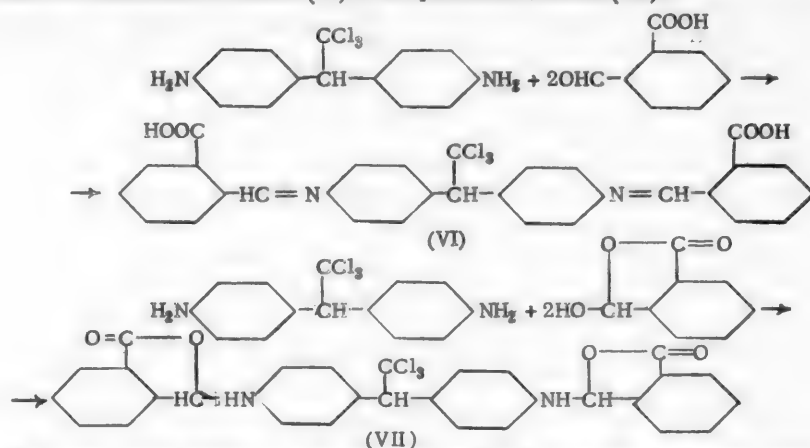
If the synthesized substances have the structure (VI), they contain an open carboxyl group, whereas if their structure is that of (VII), they possess the closed phthalide group.

To ascertain the structure of the compounds we had synthesized from phthalaldehydic and opianic acids, we investigated their behavior in solutions of alkali, soda and bicarbonate. When the soda solution is allowed to stand, part of the substance dissolves gradually. The substance recovered from the alkali or soda solution (by neutralization with acetic acid) dissolves immediately in a 5% bicarbonate solution and has a different melting point from that of the initial substance. On the basis of these properties, we believe that the compounds we have synthesized have the phthalide structure (VII), whereas the substances isolated from the alkali and soda solutions have the azomethine structure (VI). This is in complete agreement with the assertion of M. M. Shemyakin [5], that phthalaldehydic and opianic acids possess the phthalide structure in the solid state, while in the aldehydic form they react solely in a medium that promotes ionization. In view of the fact that we carried out the reaction in ethyl acetate, a medium in which no ionization takes place, it is most probable that compounds of phthalide structure are formed.

We also condensed the amine (III) with p-acetylaminophenyl sulfochloride.

We prepared the aldehyde bisulfite derivatives of the amines (III) and (V) in order to synthesize compounds that were water-soluble.

The compounds we have synthesized are listed in the following table.

EXPERIMENTAL

1,1,1-Trichloro-bis-(p-nitrophenyl)-ethane (II). 40 grams of 1,1,1-trichlorodiphenylethane, m.p. 62-64°, prepared by condensing chloral with benzene by means of sulfuric acid ($d = 1.84$), was dissolved in 120 ml of chloroform. The solution was chilled to from -10 to -5° and thoroughly stirred and chilled while a mixture consisting of 160 ml of nitric acid ($d = 1.5$) and 40 ml of sulfuric acid ($d = 1.84$) was slowly added. The acids were added at a temperature that did not exceed 0°. Then stirring was continued at room temperature for another 4 hours. The chloroform solution was removed, washed with water, and dried over calcium chloride. When the chloroform was driven off in vacuo, a viscous oil was left behind, which crystallized when a small amount of ether was added. The ether was filtered out, and the mass rewashed with ether, yielding 24-25 g of a substance. Crystallization of the latter from glacial acetic acid yielded 21-22 g of a substance with an m.p. of 164-165°, representing 40-42% of the theoretical yield. Recrystallization raised the melting point to 165-167°.

When 200 ml of sulfuric acid ($d = 1.84$) and 40 g of potassium nitrate were added to a chloroform solution of 1,1,1-trichlorodiphenylethane, the reaction resulted in the same yield, but one crystallization sufficed

to secure a pure substance with an m.p. of 166-167°.

TABLE

Compounds synthesized from the amine (III)	Compounds synthesized from the amine (V)

1,1,1-Trichloro-bis-(p-aminophenyl)-ethane (III)   The 1,1,1-trichloro-bis-(p-nitrophenyl)-ethane (II) was reduced catalytically as described in the literature [2]. The product was reprecipitated twice from its hydrochloride, its m.p. being 149-150°. The yield was 50% of the theoretical.

The 1,1,1-trichloro-bis-(p-nitrophenyl)-ethane was reduced by stannous chloride and hydrochloric acid in alcoholic solution, as described [4]. The reduction product was secured by diluting the reaction mass with water, neutralizing it with sodium acetate, and then extracting it with water. Difficulties were involved in this operation, inasmuch as vigorous agitation produced a stable emulsion. Only by means of slow and careful agitation, using large quantities of ether, were we able to extract the amine completely. The ether solution was processed with dilute hydrochloric acid (1:20). The acid solution was fractionally neutralized, a saturated solution of sodium acetate being added at first until the solution turned turbid, the precipitate thrown down being filtered out, and then more acetate being added until precipitation was complete. The resultant substance was dissolved in dilute hydrochloric acid and precipitated with sodium acetate. This yielded a substance with an m.p. of 149-151°, the yield being 90%. The amines synthesized by the two procedures were wholly identical and their mixed melting point exhibited no depression.

Found %: C 53.17; H 4.32; N 9.02; Cl 33.47. $C_{14}H_{13}N_2Cl_3$. Calculated %: C 53.33; H 4.12; N 8.88; Cl 33.80.

1,1,1-Trichloro-bis-(p-acetoaminophenyl)-ethane. When 1,1,1-trichloro-bis-(p-nitrophenyl)-ethane was catalytically reduced in acetic acid that contained a small percentage of acetic anhydride (b.p. 118-119°), and the product was neutralized, we obtained a substance that was insoluble in ether. The m.p. of the substance was 258-259° after crystallization from glacial acetic acid. When 1,1,1-trichloro-bis-(p-aminophenyl)-ethane (III) was acetylated with a mixture of acetic acid and acetic anhydride in pyridine, we obtained a substance with the same melting point (instead of 275° [2] and 245-250° [4]).

Condensing 1,1,1-trichloro-p,p'-diaminodiphenylethane (III) with aldehydes. The condensation products of the diamine (III) with aldehydes that are listed in the table were synthesized. The general procedure utilized in their synthesis was as follows: a mixture of equimolar solutions of the diamine and the aldehyde in ethyl acetate were heated to 65-70° for 2-3 hours. After the solution had cooled, a Schiff base slowly crystallized out. The yield was 80-90% of the theoretical.

As a rule, recrystallization lowered the melting points of the substance synthesized, so that we purified them by washing the synthesized compounds with alcohol, acetone, and ether.

1,1,1-Trichloro-bis-p,p'-(salicylideneaminophenyl)-ethane was synthesized from 1 mole of 1,1,1-trichloro-bis-(p-aminophenyl)-ethane (III) and 2 moles of salicylaldehyde, the yield being 75-80%. This yielded orange-yellow crystals with an m.p. of 185.5-186°. They were insoluble in water, sparingly soluble in alcohol and in ethyl acetate, and freely soluble in chloroform. They were purified by washing with alcohol and with ethyl acetate.

Found %: N 5.50; Cl 20.47. $C_{18}H_{21}N_2Cl_3O_2$. Calculated %: N 5.36; Cl 20.47.

1,1,1-Trichloro-bis-p,p'-(phthalidylaminophenyl)-ethane was synthesized by pouring together a solution of 1,1,1-trichloro-bis-(p-aminophenyl)-ethane (III) (1 mole) in ethyl acetate and a solution of phthalaldehydic acid (2 moles) in the same solvent. An abundant white precipitate settled out after 20-30 minutes of heating on a water bath. The yield was quantitative, and the m.p. 228-230°.

Found %: N 4.84; Cl 18.36. $C_{30}H_{21}N_2Cl_3O_4$. Calculated %: N 4.83; Cl 18.38.

The synthesized substance was insoluble in water or bicarbonate, sparingly soluble in alcohol, acetone, ethyl acetate, and soda, and soluble in alkali. The substance was soluble in bicarbonate after being precipitated from an alkaline solution by acetic acid.

1,1,1-Trichloro-bis-p,p'-(meconylaminophenyl)-ethane. When a benzene solution of 1 mole of 1,1,1-trichloro-bis-(p-aminophenyl)-ethane (III) was heated with 1 mole of opianic acid to 79-80° and then part of the benzene was driven off, a white powder was precipitated quantitatively, whose m.p. was 229-230° after washing with benzene, acetone, and ether.
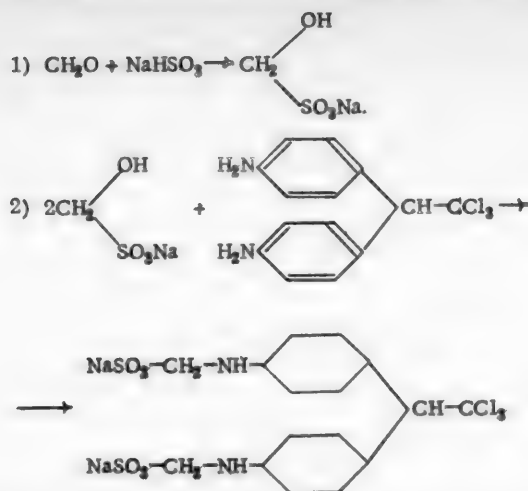
Found %: N 3.95; Cl 14.62. $C_{36}H_{29}N_2O_8Cl_3$. Calculated %: N 4.00; Cl 15.23.

The substance was insoluble in water, acetone, alcohol, ether, benzene and soda, and soluble in alkali. The substance just precipitated by acetic acid from an alkali solution and washed with water dissolved in bicarbonate.

1,1,1-Trichloro-bis-p,p'-(cotarnylideneaminophenyl)-ethane was synthesized by stirring a mixture of 1 mole of 1,1,1-trichloro-bis-(p-aminophenyl)-ethane (III) and 2 moles of cotarnine in ethyl acetate for 3-4 hours at room temperature and then allowing the solution to stand for 12-14 hours. A slightly pinkish powder was produced, its yield being almost quantitative. The substance was freely soluble in chloroform, though insoluble in water, alcohol, acetone, ether, benzene, and toluene. It was washed with alcohol and ether; its m.p. was 145.5-146°.

Found %: N 7.22; Cl 13.86. $C_{38}H_{39}N_4O_6Cl_3$. Calculated %: N 7.43; Cl 14.13.

1,1,1-Trichloro-bis-p,p'-(sodium salt of formaldehyde bisulfite-aminophenyl)-ethane. This reaction took place in two stages, as follows:

1) $CH_2O + NaHSO_3 \rightarrow CH_2(OH)(SO_3Na)$

2) $2\ CH_2(OH)(SO_3Na) + H_2N{-}\langle\text{phenyl}\rangle{-}CH{-}CCl_3({-}\langle\text{phenyl}\rangle{-}NH_2) \rightarrow$

$\rightarrow NaSO_3{-}CH_2{-}NH{-}\langle\text{phenyl}\rangle{-}CH{-}CCl_3({-}\langle\text{phenyl}\rangle{-}NH{-}CH_2{-}SO_3Na)$

2 ml of a 31.8% solution of bisulfite and 0.6 ml of 37% formalin were placed in a three-necked flask fitted with a stirrer and heated on a water bath. Five to ten minutes later, after the absence of any excess formalin had been established by means of aniline water, a solution of 1 g of 1,1,1-trichloro-bis-(p-aminophenyl)-ethane (III) in 15 ml of alcohol was added, with stirring, to the flask, which was kept at 50-60°. Stirring was continued at 60-65° for 3 hours. Then the solution was decanted from the slight precipitate. When the solution was left to stand, crystals settled, which were filtered out and washed with alcohol. This yielded 1.2 g of a substance, its yield being approximately 75%. The substance contained 2 molecules of water of crystallization.

Found %: N 7.90; S 10.84. $C_{18}H_{19}O_6N_2S_2Cl_3Na_2 \cdot 2H_2O$. Calculated %: N 7.92; S 10.90.

The substance was soluble in water, producing a transparent, slightly yellow solution. The aqueous solution is partially hydrolyzed when it is allowed to stand for a few hours in the cold, a precipitate settling out.

1,1,1-Trichloro-bis-p,p'-(sodium salt of glucose sulfonate-aminophenyl)-ethane. This was synthesized by adding 5.6 g of bisulfite (15 ml of a 37.8% solution) and 6 ml of water to 3.6 g of glucose. The resulting transparent solution was heated to 65-70° and stirred while a solution of 3.2 g of 1,1,1-trichloro-bis-(p-nitrophenyl)-ethane (II) in 50 ml of alcohol was added. Stirring and heating were continued for 4 hours. As the mixture cooled, a large quantity of an oily product settled to the bottom of the flask; it yielded a cream-colored powder when treated with absolute alcohol. The powder was suction-filtered, and 50 ml of absolute alcohol was added to the filtrate, yielding a little more of the same product. This yielded a total of 4.5 g of dry cream-colored powder. The yield was 50% of the theoretical. The substance was freely soluble in water. Concentrated aqueous solutions of the substance are faintly yellowish, while dilute solutions are absolutely colorless. The aqueous solution is unstable, hydrolyzing upon standing.

Found %: S 6.99; Na 5.25. $C_{26}H_{31}O_{16}N_2Cl_3S_2Na_2 \cdot 2H_2O$. Calculated %: S 7.24; Na 5.21.

1,1,1-Trichloro-bis-p,p'-(acetaminophenylsulfonamidophenyl)-ethane. 3 grams of p-acetylaminophenyl sulfochloride was gradually added at 0-2°, with constant stirring, to a solution of 2 g of 1,1,1-trichloro-bis-(p-aminophenyl)-ethane (III) in 10 ml of pyridine. After addition was complete, the reaction mass was heated to 40-45° for 3 hours, with stirring, and then allowed to stand overnight. The next morning the resultant solution was poured drop by drop, with stirring, into 1 liter of a 2% solution of hydrochloric acid, a flocculent pink precipitate (4 g) settling out. The substance was recrystallized from 50% alcohol, after which its m.p. was 223-224° (with decomposition). The substance was insoluble in water, though sparingly soluble in alcohol.

Found %: N 7.83; S 9.05; Cl 14.58. $C_{30}H_{27}O_6N_4S_2Cl_3$. Calculated %: N 7.90; S 9.03; Cl 15.04.

1,1-Dichloro-p,p'-bis-(nitrophenyl)-ethylene (IV) was synthesized by gradually adding 0.6 g of finely powdered potassium hydroxide to a suspension of 2 g of dinitrodiphenyltrichloroethane in 50 ml of alcohol at room temperature. The next day the precipitate was filtered out and washed with water. Crystallization

from glacial acetic acid yielded 1.6 g of a substance with an m.p. of 172-173° (90% of the theoretical yield).

1,1-Dichloro-p,p'-bis-(aminophenyl)-ethylene (V). The 1,1-dichloro-p,p'-dinitrodiphenylethylene (IV) was readily reduced with molecular hydrogen, using Raney's nickel in glacial acetic acid at room temperature and atmospheric pressure, yielding an amine with an m.p. of 144-145°. The yield was 80% of the theoretical. The reduction of 1,1-dichloro-p,p'-bis-(nitrophenyl)-ethylene (IV) with stannous chloride and hydrochloric acid proceeded like the reduction of the 1,1,1-trichloro-bis-(nitrophenyl)-ethane (II), resulting in the production of dichloro-p,p'-bis-(aminophenyl)-ethylene (V) with an m.p. of 143-145°. The yield was 90% of the theoretical. The m.p. of the amine was 144.5-145° after recrystallization from dilute alcohol.

The amines produced by the two methods — catalytically and by reduction with stannous chloride and hydrochloric acid — were entirely alike, nor did their mixed melting point exhibit any depression.

1,1-Dichloro-bis-p,p'-(salicylideneaminophenyl)-ethylene was synthesized by adding 0.9 g of salicyl-aldehyde to a solution of 1 g of the unsaturated amine (V) in 20 ml of ethyl acetate. The solution was heated to 65-70° for 2 hours, its color rapidly turning orange. When it cooled 1.2 g of orange-colored crystals settled out. Evaporation of the filtrate yielded another 0.4 g of the substance. The yield of the pure product was 80% of the theoretical. The substance was soluble in chloroform, sparingly soluble in alcohol, ethyl acetate, and ether, and insoluble in water. Its m.p. was 191-193° after washing with alcohol and ether.

Found %: N 5.83; Cl 14.60. $C_{28}H_{20}O_2N_2Cl_2$. Calculated %: N 5.76; Cl 14.61.

1,1-Dichloro-bis-p,p'-(phthalidylaminophenyl)-ethylene. A solution of 1 g of phthalaldehydic acid in 30 ml of ethyl acetate was added to a solution of 1 g of 1,1-dichloro-p,p'-bis-(aminophenyl)-ethylene (V) in 10 ml of ethyl acetate, and the mixture was heated to 60-65° for 3 hours. The precipitated substance was dried and washed with ethyl acetate, alcohol, and ether, after which its m.p. was 250-251° (with decomposition). The yield totaled 5 g (90% of the theoretical).

Found %: N 5.28; Cl 12.97. $C_{30}H_{20}O_4N_2Cl_2$. Calculated %: N 5.15; Cl 13.07.

The substance was soluble in 2% alkali, though insoluble in 15% bicarbonate. The substance dissolved instantly in bicarbonate after it had been precipitated from an alkali solution by neutralization with acetic acid. Its m.p. was 218-220° (with decomposition).

1,1-Dichloro-bis-p,p'-bis-(meconylaminophenyl)-ethylene. A solution of 1.5 g of opianic acid in 30 ml of ethyl acetate was added to a solution of 1 g of 1,1-dichloro-p,p'-bis-(aminophenyl)-ethylene (V) in 30 ml of ethyl acetate, and the resultant solution was heated to 65-70° for 2 hours. A white precipitate was thrown down; it was filtered out and washed with ethyl acetate, alcohol, and ether, after which its melting point was 219-221°. The substance was soluble in alkali, and insoluble in bicarbonate.

Found %: N 4.32. $C_{34}H_{28}O_8N_2Cl_2$. Calculated%: N 4.22.

1,1-Dichloro-bis-p,p'-(sodium salt of formaldehyde bisulfite-aminophenyl)-ethylene was synthesized like the formaldehyde bisulfite derivative of 1,1,1-trichloro-bis-(p-aminophenyl)-ethane (III) at 70-75°, the yield being 80% of the theoretical. The substance was crystallized from 80% alcohol. Its aqueous solutions are transparent and unstable upon standing. The substance can be kept for 2-3 weeks in a dry, closed, dark place, rapidly darkening and decomposing when exposed to the open; it contains two molecules of crystallization water.

Found %: S 12.05; Na 8.53. $C_{16}H_{14}O_2N_2Cl_2S_2Na_2 \cdot 2H_2O$. Calculated %: S 11.72; Na 8.42.

1,1-Dichloro-bis-p,p'-(sodium salt of glucosesulfonate-aminophenyl)-ethylene was synthesized like the glucoside sulfonate derivative of 1,1,1-trichloro-bis-(p-aminophenyl)-ethane. It was a faintly cream-colored powder after it had been processed with absolute alcohol. The yield was 60% of the theoretical. The substance was freely soluble in water. Concentrated solutions are slightly yellowish, dilute solutions being colorless. Aqueous solutions are unstable when stored.

Found %: N 3.12; S 7.63; Na 5.45. $C_{26}H_{34}O_{16}N_2Cl_2S_2Na_2 \cdot 2H_2O$. Calculated %: N 3.30, S 7.55; Na 5.43.

SUMMARY

1. A method has been developed for nitrating 1,1,1-trichlorodiphenylethane.

2. 1,1,1-trichloro-p,p'-diaminodiphenylethane (III), with an m.p. of 149-150°, has been synthesized, the yield being 90% of the theoretical.

3. Reducing 1,1,1-trichloro-p,p'-dinitrodiphenylethane and 1,1-dichloro-p,p'-dinitrodiphenylethylene in glacial acetic acid that contained acetic anhydride produced high yields of the acetyl derivatives of the respective amines.

4. The structure of the synthesized nitro amino compounds has been established as that of p,p' substitution derivatives of diphenyltrichloroethane and diphenyldichloroethylene.

5. Twelve compounds, four of which are water-soluble, have been secured from 1,1,1-trichloro-p,p'-diaminodiphenylethane and 1,1-dichlorodiaminodiphenylethylene and have been identified.

6. Contrary to foreign findings that 1,1,1-trichloro-p, p'-diaminodiphenylethane and its ethylene derivative are highly active tuberculostatically, these compounds were found to be only slightly active.

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ALKYLATION OF AROMATIC COMPOUNDS IN THE PRESENCE OF PHOSPHORIC ACID

THE POLYALKYLATION OF PHENOL

N. G. Sidorova

In the alkylation of aromatic compounds the principal objective, as a rule, is the synthesis of monoalkyl derivatives. The reason for this is that more research has been done on monoalkylated products, and they are, therefore, more widely used. Moreover, research on the process and on the reaction products is itself simpler. This also holds true of the alkylation of phenols. It is asserted in some papers that di- and trialkylphenols have been obtained, but there is only one paper specially devoted to the synthesis and a study of the properties of some trialkylphenols [1].

We have made a study of the polyalkylation of phenol with n-butyl and isobutyl alcohols in the presence of phosphoric acid. In our laboratory we have more than once shown [2] that phosphoric acid is superior to other condensing agents in the alkylation of phenol by alcohols. When equimolecular quantities of the alcohol and phenol are used in condensation with phosphoric acid we get satisfactory yields of pure monoalkylated phenols, whereas many other catalysts produce a mixture of products of varying degrees of substitution. By using phosphonic   acid we hoped to ascertain whether two or three alkyl groups can be introduced during alkylation as desired. We took the corresponding quantities of alcohol and phenol to guide the reaction along the desired course, besides increasing the intensity and duration of the heating.

In the condensations with n-butyl alcohol we managed to find the conditions required for obtaining a compound with the desired degree of substitution as the principal product. We used 2 moles of n-butyl alcohol and 400 ml of phosphoric acid (d = 1.86) per mole of phenol to introduce 2 butyl groups; heating lasted 11 hours at 130-150°. The aggregate yield of disubstituted products (dibutylphenol and the butyl ether of butylphenol) was 70% of the theoretical. We accordingly used 3 moles of the alcohol and 600 ml of phosphoric acid to introduce three groups, heating to 140-160° being continued for 23 hours. The yield of trisubstituted products was 70% of the theoretical.

The reaction with isobutyl alcohol did not proceed nearly as satisfactorily under these conditions, although isobutyl alcohol enters into condensation reaction more readily, as we know. This is apparently due to the fact that the alkylation reaction is paralleled by the reverse reaction: dealkylation, the two reaction rates being governed by the temperature. As the temperature is raised, the rate of alkylation rises, though the rate of dealkylation rises still faster when a certain temperature is exceeded. When the temperature is kept low, we can expect to keep the reverse reaction to a minimum. As a matter of fact, we were able to improve the yield of polybutylphenols somewhat by lowering the temperature. The reactions with isobutyl alcohol were run with the same reagent proportions and heating time as those used for n-butyl alcohol, but the reaction temperature was varied. Dialkylation was performed at 140°, the yield of dialkylated products totalling 45% of the theoretical. Trialkylation at 110-120° yielded 37% of tributylphenol, whereas performing this same reaction at 140-160° yielded only 25% of the trisubstituted product. In all the isobutyl alcohol condensations a high percentage of a monosubstituted product was formed, in addition to the polybutylphenols. Cutting the heating time to 8 hours (125-135°) results in the monosubstituted product predominating in the reaction products, with no tributylphenol present at all. By way of making a more detailed study of the polyalkylation process, we tried to perform this reaction step by step, in the thought that when the alkyl groups were introduced gradually the reaction would be smoother, yielding the desired product completly.   With this as our objective we condensed p-tert-butylphenol with isobutyl alcohol. But when the second alkyl group was introduced, we found that the reaction was not as smooth as when the first group was added. This is most likely due to parallel dealkylation.

According to the findings of Stilson and his associates [1], trialkylphenols that contain tertiary radicals do not dissolve at all in aqueous alkalies or in a solution of potassium hydroxide in methanol. Trialkylphenols that contain secondary radicals are insoluble in aqueous solutions of alkalies, but do dissolve in alcoholic solutions of potassium hydroxide. The solubility of dialkylphenols in these solutions depends upon the nature of the alkyl groups and their positions. We utilized aqueous solutions of alkalies of varying concentrations to separate the dialkylphenols from the phenol ethers. The condensation products of n-butyl alcohol can be readily separated by means of strong (20-30%) solutions of alkali. Tributylphenol is wholly insoluble in such a solution. With the isobuytl alcohol it is best to use dilute alkali solutions (5-10%).

In the light of the conditions governing their recovery the trisubstituted products might be regarded as a mixture of tributylphenol with butyl ethers of the dibutyl-phenols. Determination of the hydroxyl groups indicated, however, that the substances were 100% phenols. It is evident that distillation entailed the isomerization of the phenol ethers to aklyl phenols.

The di-and tributylphenols were obtained as oily liquids that did not crystallize upon standing, which was due, apparently, to the formation of a mixture of isomers with differing radical structures. It is very difficult to purify the di- and tributylphenols, since they are dealkylated appreciably when distilled, even in vacuo. Analysis of the collected fractions indicates that substances of a lower degree of substitution are present.

We did not investigate the phenol ether fractions, since they were partially isomerized to the corresponding alkylphenols when distilled.

EXPERIMENTAL

The phosphoric acid ($\underline{d}$ = 1.86) utilized in our condensations was prepared by evaporating commerical phosphoric acid with some nitric acid in a platinum cup. After the acid had cooled, it was diluted with distilled water to the required strength. The use of glass or porcelain vessels in evaporating the phosphoric acid contaminates it with impurities that diminish its activity.

Condensation was performed in a three-neckedflask, using mechanical stirring. A mixture of phenol and phosphoric acid was heated to the required temperature, and the alcohol was added from a dropping funnel, after which stirring and heating were continued. The reaction temperature was checked by means of a thermometer immersed in the reaction mixture.

When the reaction was over, the mixture was diluted with water, the upper layer being removed and processed a few times with an alkali solution. The alkali solutions were combined, and the phenols extracted from them by the action of hydrochloric acid. The precipitated phenols were washed with water until their reaction was neutral, dried over calcium chloride, and distilled.

The portion of the alkylation products (the tributylphenols and the butyl ethers of the mono- and dibutylphenols) that was insoluble in the alkali was likewise washed with water until its reaction was neutral, dried over calcium chloride, and fractionated. Broad fractions were collected, the yield being calculated in terms of these crude products. The corresponding fractions of similar condensations were combined together and repeatedly distilled in vacuo and at ordinary pressure. The isolated narrow fractions of phenols constituted mixtures of isomers. They were identified only by their analyses and their constants, inasmuch as no derivatives of di- and tributylphenols can be prepared under ordinary conditions. No investigation was made of the nonphenolic part of the condensation products.

Condensation of phenol with n-butyl alcohol. The condensation conditions and results are listed in Table 1.

Redistillation of the 245-270° phenolic fraction yielded the dibutylphenol (a mixture of isomers).

B.p. 257-265°; d_4^{21} 0.9445; n_D^{21} 1.5100; MR_D 65.08; calculated 64.78.

0.1302 g substance: 0.3868 g CO_2. 0.1179 g H_2O. 0.2188 g substance: 30.2 ml CH_4 (29°, 718 mm). Found %: C 81.02; H 10.06; OH 8.40, $C_{14}H_{22}O$. Calculated %: C 81.55; H 10.68; OH 8.25.

The 270-290° fraction yielded the tributylphenol (a mixture of isomers).

B.p. 275-279°; d_4^{21} 0.9373; n_D^{21} 1.5074; MR_D 83.3; calculated 83.25.

0.0908 g substance: 0.2745 g CO_2; 0.0896 g H_2O. 0.2126 g substance: 25.9 ml CH_4 (29°, 718 mm); Found %: C 82.45; H 10.96; OH 7.45. $C_{18}H_{30}O$. Calculated %: C 82.44; H 11.45; OH 6.49.

TABLE 1

Results of Condensing n-Butyl Alcohol with Phenol

Condensation number	Original substances				Time hours	Product yield			
	Phenol	Alcohol	Ml of H_3PO_4	Temperature		From the alkali solution		Portion insoluble in alkali	
						Butylphenol b.p. 220-245°	Dibutylphenol b.p. 245-270°	Butyl ether of butylphenol, b.p 245-270°	Tributylphenol b.p. 270-295°
1	23.5 g (0.25 mole)	37 g (0.5 mole)	100	130-150°	11	9.5 g (9%)	14.5 g (28%)	21.6 g (42%)	4.6 g (7%)
2	23.5 g (0.25 mole)	55 g (0.75 mole)	150	140-160	23	—	—	—	46 g (70%)

TABLE 2

Condensation No.	Original substances			Temperature	time hours	Product yield					
	Phenol	Alcohol	Ml of H_3PO_4			From the alkali solution			Portion insoluble in alkali		
						Butylphenol, b.p. 220-245°	Dibutylphenol, b.p. 245-265°	Tributylphenol b.p. 265-280°	Butyl ether of phenol 220-245°	Butyl ether of dibutyl phenol, b.p. 245-265°	Tributylphenol b.p. 265-280°
1	47 g (0.5 mole)	74 g (1 mole)	200	135-145°	11	8 g (10.7%)	33 g (32%)	7.5 g (6%)	—	13 g (12.6%)	8.9 g (7%)
2	23.5 g (0.25 mole)	55 g (0.75 mole)	150	125-135	8	17 g (46%)	—	—	6.3 g (17%)	17.5 g (34%)	—
3	23.5 g (0.25 mole)	55 g (0.75 mole)	150	140-160	22	5.1 g (13.6%)	15.7 g (30.5%)	4.6 g (7%)	4.3 g (11.5%)	4.0 g (7.8%)	11.5 g (17.6%)
4	23.5 g (0.25 mole)	55 g (0.75 mole)	150	110-120	22	6.5 g (17.4%)	4.5 g (8.7%)	—	3.3 g (9%)	6.0 g (11.6%)	24.2 g (37%)

The fraction constituting the butyl ether of butyl phenol dissolved partially in potassium hydroxide after distillation, indicating that isomerization to dibutylphenol had taken place.

Condensing phenol with isobutyl alcohol. The condensation conditions and results are listed in Table 2.

The 220-245° phenolic fractions crystallized in part upon standing. The precipitated crystals had an m.p. of 99° after recrystallization from water, which is the m.p. of p-tert-butylphenol.

Redistillation of the 245-265° phenolic fractions yielded the dibutylphenol (a mixture of isomers).

B.p. 255-262°; d_4^{22} 0.9538; n_D^{22} 1.4965; MR_D 63.16; calculated 64.78.

0.1130 g substance: 0.3366 g CO_2; 0.1024 g H_2O. Found %: C 81.24; H 10.07; $C_{14}H_{22}O$. Calculated %: C 81.55; H 10.68.

Distillation of the 265-280° fractions yielded a product with a b.p. of 275-280°; d_4^{22} 0.9488; n_D^{22} 1.4965. Analysis of this product indicated that it consisted largely of low-molecular phenols.

SUMMARY

1. The polyalkylation of phenol by n-butyl and isobutyl alcohols in the presence of phosphoric acid

has been investigated.

2. In the case of n-butyl alcohol the conditions have been discovered that make it possible to introduce two or three butyl groups into the phenol molecule (with yields up to 70% of the theoretical). The reaction is not complete when isobutyl alcohol is used owing to the parallel dealkylation that takes place.

3. The condensations yield a mixture of alkylphenols and phenol ethers. The di- and tributylphenols are partially dealkylated during distillation.

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THE ALKYLATION OF AROMATIC COMPOUNDS BY ALCOHOLS IN THE PRESENCE OF ALUMINUM CHLORIDE

XV.* THE ALKYLATION OF BENZENE IN A CONTINUOUS-ACTION APPARATUS

I. P. Tsukervanik and Kh. Taveeva

In some recent reports by A. V. Topchiev and his associates [1] the authors have described the alkylation of benzene and of saturated hydrocarbons with the new catalyst $BF_3 \cdot H_3PO_4$ in a continuous-action apparatus. This alkylation method cuts down the formation of polyalkyl derivatives; in our reactions using $AlCl_3$ we may also look forward to an appreciable diminution of the side reactions of cleavage and isomerization of the alcohol radicals as the result of the action of the $AlCl_3$ or of its coordination compounds. Changing the apparatus described by A. V. Topchiev, and his associates [1] somewhat, we used it to alkylate benzene with isopropyl, n-butyl, and ethyl alcohols reactions which had been previously investigated in our laboratory. In the apparatus reactor there gradually accumulated a heavy, oily "lower layer" that contained $AlCl_3$, the products of its interaction with alcohol, and various by-products (polyalkylated derivatives, olefins and others) in the shape of coordination compounds with $AlCl_3$. Rapidly removing the normal reaction products from this layer ought to improve the results of alkylation. By using syphoning from the reactor to the distilling flask, we achieved complete separation of the reaction mixture from the lower layer. But when the excess benzene was driven off from the decanted colored mixture, an oily lower layer again separated out. Still, we believe that the influence of the excess $AlCl_3$ and of the lower layer has been greatly reduced in the experiments we have carried out.

According to our earlier findings [2], alkylating benzene with isopropyl alcohol yielded up to 70% of alkylbenzenes, though the mixture contained a large percentage of di- and polyisopropylbenzenes. Condensation in the apparatus with 0.6 mole of $AlCl_3$ per mole of C_3H_7OH yielded 66.5% of alkylbenzenes; the mixture of crude products contained almost no high-boiling fractions, proving to be pure cumene.

In our previous experiments [2] on the alkylation of benzene with n-butyl alcohol, we secured negligible yields of butylbenzene. The reactions were carried out with only 1.2-2 moles of $AlCl_3$ per mole of the alcohol at temperatures above 100°; under these conditions most of the alcohol underwent cleavage. When small quantities of $AlCl_3$ were used on a water bath, no perceptible yields of butylbenzene were obtained. We then ran a new series of tests on the alkylation of n- C_3H_7OH in the apparatus. We varied the quantity of $AlCl_3$, the temperature, and the order in which the reagents were added. We found that at least 1.2 moles of $AlCl_3$ were required per mole of the alcohol, as had been demonstrated earlier [3]; however, the reaction takes place in the apparatus at 75-80°, yielding about 35% of the theoretical (based on the alcohol used) of the monobutylbenzenes. The reaction mixture contains practically no polyalkylbenzenes. We made an approximate determination of the amount of unreacted n-butyl benzene in the wash waters by measuring the refractive index; subsequent calculation indicated that the butylbenzene yield was 60% of the theoretical, based on the reacted n-butylbenzene. The resultant butylbenzene proved to be a mixture of isomers, with sec-butylbenzene predominating.

When we alkylated benzene with ethyl alcohol in the past [4], we always obtained a high yield (as high as 90% of the theoretical) of a mixture of hydrocarbons, the ethylbenzene yield never exceeding 35-40%, di- and polyethylbenzenes predominating. This result was obtained when we used 2 moles of $AlCl_3$ per mole of alcohol and heated the mixture for 10 hours on an oil bath (120-130°). Alkylation tests with ethyl alcohol run in the apparatus indicated that the specified quantity of $AlCl_3$ is actually required to secure high product yields. The reaction proceeds faster and at a lower temperature in the apparatus. Heating the mixture for 2 hours on a water bath yielded 85% of the theoretical yield of alkylbenzenes; the mixture of reaction products

yielded a total of 25-30% of the theoretical yield of ethylbenzene, the bulk of the product consisting of di- and polyethylbenzenes. In these condensations we always observed the formation within the reactor of an oily lower layer , which contained polyethylbenzenes, as was proved by a special test. It is evident that the alkylation products are selectively extracted by the lower layer [5], under our reaction conditions, resulting in the specified condensation results. Hence, there is no advantage to be gained by ethylating benzene in the device over the usual method of performing these condensations, as far as the composition of the reaction products is concerned.

EXPERIMENTAL

The following modifications were made in the apparatus described by A. V. Topchiev and his associates [1]. The reactor was fitted with an auxiliary tube for gradually supplying the $AlCl_3$. The motor-driven stirrer was replaced by a magnetic stirrer. The overflow tube was made of two glass sections connected together by rubber tubing fitted with a clamp; the end of the tube that was lowered into the distilling flask was drawn out to a narrow tip (2 mm diameter); all this made it possible to regulate the overflow of the transparent reaction mixture better.

Benzene-isopropyl alcohol. 43 grams (0.32 mole) of $AlCl_3$ was gradually added to a mixture of 150 ml of benzene and 30 g (0.5 mole) of C_3H_7OH in the reactor. Then the mixture was heated on a water bath (75°) for 2 hours and left to stand at room temperature for 12 hours. Then we began to drive the benzene (200 ml) out of the distilling flask. At the same time that the benzene entered the mixture of products was decanted from the reactor to the distilling flask; this took 2 hours.

After the usual processing, we obtained the following fractions: 2.3 g at 80-145°; 37.6 g at 145-202°; and 1.2 g of residue. Redistillation of the first two fractions yielded 37 g of cumene, with the following constants [6]: b.p. 148-152° (730 mm); d_4^{20} 0.8731; n_D^{20} 1.4942.

Benzene-n-butyl alcohol. We took 300 ml of benzene, 25 g (0.33 mole) of n-C_4H_9OH, and 55 g of $AlCl_3$ (0.42 mole). After the $AlCl_3$ had been added, the mixture was heated to 75° for 3 hours; then we began to siphon from the reactor to the distilling flask and drive the benzene into the reactor (3 hours). The fractions collected were: 15.5 g at 140-180° (butyl-benzene, 34% of the theoretical); 0.7 g at 180-190°; and 1.3 g of residue.

The reaction mixture was thoroughly washed with an excess of acidulated water to determine the percentage of unreacted butyl alcohol. The collected wash waters were alkalinized and then brought to 1 liter. Then the refractive index of a distilled portion (100 ml) of the wash waters was determined. It was found to be n_D^{27} 1.3350, equivalent to some 1.1% of n-butyl alcohol (determined in a control experiment), whence the unreacted n-C_4H_9OH totaled 11 g: hence, the butylbenzene yield was about 60%, based on the reacted n-C_4H_9OH.

Repeated distillations of the crude butylbenzene yielded a 168-170° (730 mm) fraction; d_4^{20} 0.8603; n_D^{20} 1.4912; MR_D 45.14.

These fractions had constants that approximated those of sec-butylbenzene [6,7]; the slight deviation from the values in the literature is evidently due to the presence of a slight amount of n-butylbenzene. We determined the approximate percentage of n-butylbenzene graphically, using the data in the refractive indexes of the isomeric butyl-benzenes. The sec-butylbenzene totaled about 15%. Lastly, we secured an acetamino derivative with an m.p. of 127° [7] to identify the sec-butylbenzene.

Benzene-ethyl alcohol. We used: 300 ml of benzene, 16 g (0.33 mole) of alcohol, and 87 g (0.66 mole) of $AlCl_3$. The mixture was heated on a water bath for 2 hours. Syphoning lasted 3 hours. The lower layer was separated from the benzene layer for processing and decomposed separately with water. The following fractions were collected: from the benzene layer: 0.2 g at 90-110°; 3.2 g at 110-150°; and 0.2 g of residue; from the lower layer: 5 g at 110-150°; 7.1 g at 150-200°; 32 g at 200-250°; and 4.3 g of (crystalline) residue.

Repeated distillations of the 110-150° fraction yielded ethylbenzene with a b.p. of 134-135° (730 mm); d_4^{20} 0.8675; n_D^{20} 1.4959.

SUMMARY

1. A study has been made of the alkylation of benzene with alcohols and $AlCl_3$ in a continuous-action apparatus.

2. Isopropyl alcohol yielded cumene, the yield being 60% of the theoretical.

3. This method of condensation made it possible for the first time to effect the butylation of benzene with $\underline{n}$-C_4H_9OH with a satisfactory yield (as high as 60% of the theoretical, based on the reacted alcohol).

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THE RELATIONSHIP OF THE STRUCTURE OF HYDROXYAZO DYES TO THEIR ABILITY TO CHANGE COLOR AT THE SURFACE OF MAGNESIUM HYDROXIDE

L. M. Kulberg

Among the reagents for magnesium there is a large group of hydroxyazo dyes, all of which change color at the surface of magnesium hydroxide characteristically at the instant of its formation. The hydroxyazo dyes that exhibit this reaction can be divided into two groups. One group includes the p-nitro- and o-nitrohydroxyazo dyes with the following general formula:

$$O_2N-\langle\ \rangle-N=N-ROH\ (P,\ o);$$
$$(NO_2)$$
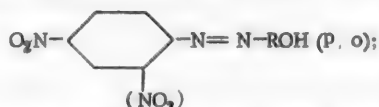
the other including the hydroxyazo dyes that do not contain a nitro group (or else have it at the meta position).

The interaction of the first group of dyes with magnesium hydroxide has been exhaustively investigated by us previously [1]; we found that the reaction involves the stabilization of the isonitro form of the dye [2] at the surface of the magnesium hydroxide as follows:
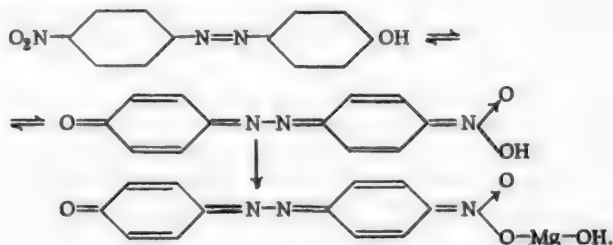
As for the second group, practially no research is found in the literature on their interaction with magnesium hydroxide [3,4].

The author, who has pointed out that dyes of the first type can be utilized as reagents for magnesium, believes   that they owe their reactivity to their hydroxyl groups [5]:


$$R_2 = H,\ CH_3,\ OCH_3.$$
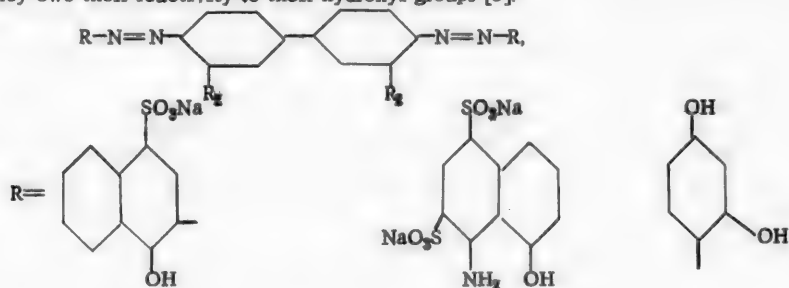
We know that the o-hydroxyazo dyes form inner coordination compounds with metals very readily, with the aryl group in the trans position to the azo group [6]:

$$\left[\underset{\text{structure}}{\text{N=N—Ar}}\right]_n \text{Me}^{n+}$$

(structure showing a ring with N=N, Ar group, O, bracketed with subscript n and Me^{n+})
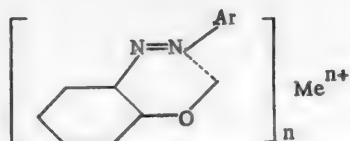
This led us to conjecture that the interaction of this group of dyes with magnesium hydroxide entails the formation of an intramolecular compound [3], such as:

(structure showing ring with N=N, cyclohexyl, Mg—OH, O, and R— substituent)
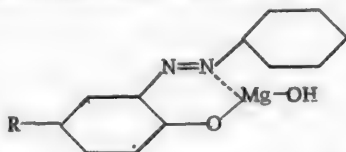
followed by its fixation at the surface of the magnesium hydroxide. We may, therefore, suppose that o-hydroxyazo dyes of the following general formula:

(structure showing N=N and OH on a ring)
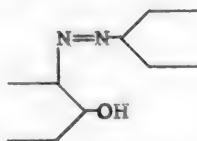
must be reactive to the magnesium ion (that is, change color characteristically at the surface of the Mg(OH)_2 at the instant the latter is formed).

Obviously, the p-hydroxyazo dyes, which do not form intramolecular compounds, should not color Mg(OH)_2 under these conditions.

The results of our tests of the p-hydroxyazo dyes at our disposal are listed in Table 3.

To prove that our assumption concerning the structure of the hydroxyazo dyes, which ensures their reactivity with Mg(OH)_2, was correct, we synthesized a number of o-hydroxyazo dyes and tested their ability to change color in an alkaline medium when Mg^{2+} is present (Table 1). All the dyes listed in the table were synthesized [1] and identified by the usual methods. The dyes that contain chromotropic and H acids as azo components were not isolated in the solid state, but were identified by their absorption spectra.

In the reactions we used 0.1% alcoholic solutions of the dyes (an aqueous-alcoholic solution being used for a dye that was insoluble in alcohol), a 1% solution of chemically pure magnesium sulfate heptahydrate, and a 1N solution of sodium hydroxide (a 0.1 N solution of sodium hydroxide being used when testing dyes that contain chromotropic acid residues). 0.25 ml of the dye solution and 1 ml of the alkali solution were added to 1 ml of the magnesium sulfate solution.

We used a solution containing 0.25 ml of a solution of the same dye, 1 ml of the alkali solution, and 1 ml of water as a control.

As we see from these findings, all the tested o-hydroxyazo dyes change their color more or less pronouncedly when Mg(OH)_2 is present at the instant the latter is formed thus conforming to the hypothesis advanced. These findings agree with Kuznetsov's observations [4] on the reaction of several azo dyes with Li^+, Ca^{2+}, and Mg^{2+} ions.

The azo dyes that contain chromotropic and H acids are of the greatest practical interest as reagents for magnesium. These dyes exhibit the most marked change in color during the course of the reaction.

Thus, among the hydroxyazo dyes that can change color at the surface of Mg(OH)_2 we encounter two functional-analytical groups that give rise to reactions with the Mg^{2+} in an alkaline medium that are of the same type externally speaking, but differ fundamentally as far as their mechanisms are involved:

---

[1] The diazo and azo components were always coupled in a slightly alkaline medium.

TABLE 1
Color of Alkaline Solutions of o-Hydroxyazo Dyes with and without Magnesium Salts
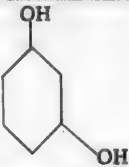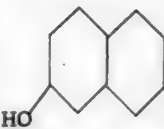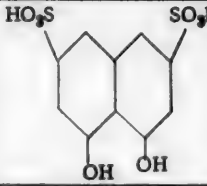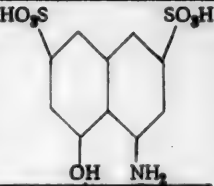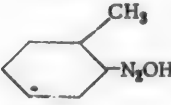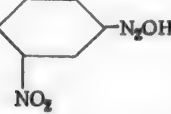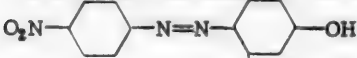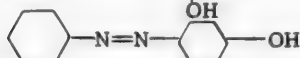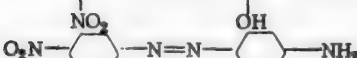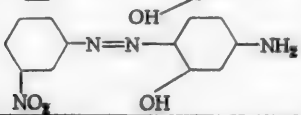
Diazo component	Azo Component							
	OH/OH		HO/OH		HO_3S / SO_3H OH OH		HO_3S / SO_3H OH NH_2	
	K[1]	M^{z+}[2]	K	Mg^{2+}	K	Mg^{2+}	K	Mg^{2+}
(phenyl)—N_2OH	Pink	Yellow	Pink	Yellow	–	–	–	–
(o-CH_3 phenyl)—N_2OH	–[3]	–	Pink	Brown	Pink	Sky-blue	Pink	Violet
H_3C—(phenyl)—N_2OH	Red	Chestnut	Yellow	Orange	Yellow	Orange	Blue	Violet
(COOH phenyl)—N_2OH	Pink	Yellow	Yellow	Pink	Pink	Crimson	Pink	Crimson
HO_3S—(phenyl)—N_2OH	Yellow	Lilac-red	Yellow	Orange	Pink	Violet	Red	Violet
(NO_2 phenyl)—N_2OH	Yellow	Lilac-red	Red	Orange	Red	Blue	Blue	Lilac
HO_3S—(naphthyl)—N_2OH	Orange	Crimson	Orange	Crimson	Red	Blue	Pink	Violet

TABLE 2
Effect of the Structure of o-Hydroxyazo Dyes Upon the Mechanism of the Reaction with Mg^{2+}

Formula of dye	Color of a weakly alkaline solution of the dye	Color of the same solution in the presence of:	
		Mg^{2+}	Acetone
O_2N—(ring)—N=N—(ring)—OH, OH	Red-brown	Blue	Blue
(ring)—N=N—(ring)—OH, OH, NO_2	Pink-yellow	Lilac-red	Pink-yellow
O_2N—(ring)—N=N—(ring)—NH_2, OH	Lilac-red	Blue	Blue
(ring)—N=N—(ring)—NH_2, NO_2, OH	Yellow	Lilac-red	Yellow

[1] Color of the control solution. [2] Color when magnesium salt is present. [3] Dye not tested

1025
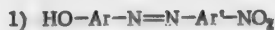
1) $HO-Ar-N=N-Ar'-NO_2$
   (p, o)   (p, o)
Intramolecular rearrangement with stabiliza-
tion of the isonitro form at the $Mg(OH)_2$
surface

2)

The behavior of the o-hydroxyazo dyes that are reagents for Mg^{2+} with acetone is a criterion of the reaction mechanism. If the
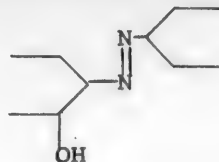
Formation of an inner complex salt which is stabilized at the $Mg(OH)_2$ surface

action of acetone causes a change in the color of an alkaline solution of the dye, like that occurring when a magnesium salt is present, it is an indication of the isomerization of the dye to the isonitro form. The absence of this effect is evidence that an intramolecular compound has been formed. The data set forth in Table 2 illustrates the foregoing.

TABLE 3

Nature of the Interaction of p-Hydroxyazo Dyes with Mg^{2+} in an Alkaline Medium

Formula of the dye	Color of the alkaline solution of the dye	Color of the same solution when $Mg(OH)_2$ is present
HO—⬡—N=N—⬡—SO₃Na	Red	Red
HO—⬡—N=N—⬡	Brown	Brown
HO—⬡—N=N—⬡ (N)	Brown	Brown
HO—⬡—N=N—⬡—SO₃Na . . . . . (N)	Red	Red

SUMMARY

1. It has been shown that hydroxyazo dyes that do not have a nitro group in the para or ortho position to the azo group react with Mg^{2+} in an alkaline medium only when they have a hydroxy group in the ortho position to the azo group.

2. The hypothesis is put forward that the reaction between the foregoing dyes and magnesium salts in an alkaline medium involves the formation of inner complex salts.

3. This hypothesis has been confirmed by a study of the reaction of several synthesized dyes with magnesium salts in an alkaline medium.

4. A criterion is given for establishing the mechanism of the reaction of o-hydroxyazo dyes with Mg^{2+} in an alkaline medium.

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THE DISSOCIATION OF HEXAPHENYLETHANE AND SIMILAR COMPOUNDS IN SOLUTIONS

D. A. Pospekhov

Waters [5] has expressed the following opinion on the dissociation of hexaphenylethane and related compounds in solutions: "Formation of neutral radicals when bonds in organic compounds are dissociated may be expected to occur only in a few solvents with low dielectric constants," and he has asserted that such solvents as ethyl alcohol ($\varepsilon = 25$), nitrobenzene ($\varepsilon = 36$), and the like, promote ionization. This view constitutes a parallel to the Nernst-Thomson rule in the electrochemistry of solutions: the higher the dielectric constant of a solvent the greater will be its dissociating power [3,7,11,12]. (Waters did not notice this parallel). The rule has been discussed frequently [1-4, 6, 7, 13-15]. The limits of its applicability have been commented upon. Some authors have considered the rule to be false [2, 3, 6]. In Walden's works on nonaqueous solutions of electrolytes [13-15], he insisted upon the correctness of the rule, but in his book on free radicals [17] he did not discuss the formation of the latter as related to the ε of the solvent.

We shall show that the experimental data now available do not bear out the cited opinion of Waters. The table below lists data [18] on hexaphenylethane, supplemented by information on the ε of the solvent. The order in which the solvents are listed in the original paper has been modified somewhat: they are here grouped in classes. As we see from the table, the heats of dissociation of all the solvents, even including proprionitrile ($\varepsilon = 27.7$), are about the same; hence there are no grounds for the belief that free radicals are formed in some solvents and ions in others.

TABLE

Solvent	Dissociation constant $K \cdot 10^4$ at 20°	Heat of dissociation Q, kcal.	Solvent's, ε
Hydrogen sulfide	19.2	11.0	2.64
Chloroform	6.9	10.5	5.05
Ethylene bromide.........................	3.9	11.4	6.3
Proprionitrile	1.2	11.1	27.7
Benzene..................................	4.1	11.3	2.3
Bromobenzene............................	3.7	11.5	5.4
Acetophenone............................	1.70	11.5	18.3
Ethyl benzoate	1.67	12.0	6.2
Dioxane..................................	2.5	11.6	2.2

We see from the table that in aliphatic solvents the lower the ε of the solvent, the higher its dissociation constant, i.e., we see somewhat of a contradiction to what Waters asserted. The same rule holds in the aromatic solvents, with the exception of acetophenone. Dioxane, as the sole heterocyclic compound, cannot be compared with anything else.
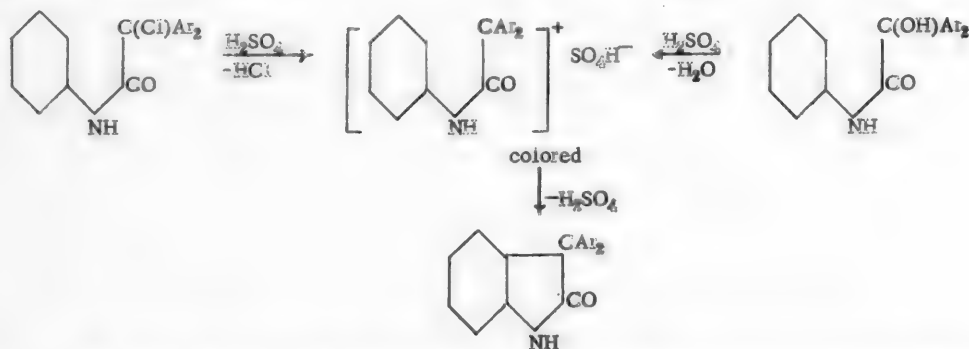
This regularity is not fortuitous, inasmuch as we know of similar facts: tetraphenyldibenzoyltetrazane $(C_6H_5)_2N-N-N-N(C_6H_5)_2$ has the following values of $K \cdot 10^4$ at -18°: 2.75 in ether ($\varepsilon=4.3$), 2.36 in chloroform $C_6H_5-CO \quad CO-C_6H_5$ ($\varepsilon =5.05$); and 1.48 in acetone ($\varepsilon = 21.4$) [8].

As opposed to Waters' opinion, solutions of hexaphenylethane in nitrobenzene are nonconductors [10]. (Solutions of triphenylmethyl in liquid sulfur dioxide ($\varepsilon = 15.6$) are conductors, owing to the formation of salt-like solvates [5, 6, 17].

OCH$_3$

CH$_3$O

CH$_3$O — NH—CO—C—OH

CH$_3$O

OCH$_3$

(VI)
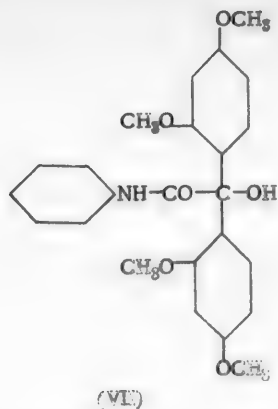
was also confirmed in the reaction of the amide and the β-naphthalide of diphenylchloroacetic acid with concentrated sulfuric acid. The structure of the resulting compounds was established by means of the following schema:

C(Cl)Ar$_2$ H$_2$SO$_3$ CAr$_2$ SO$_4$H$^-$ H$_2$SO$_3$ C(OH)Ar$_2$
CO   −HCl →   CO   +   ← −H$_2$O   CO
NH   NH   NH

colored
↓ −H$_2$SO$_4$

CAr$_2$
CO
NH

These examples established the ability of the aryl amides of diphenylchloroacetic acid to enter into intramolecular condensations, yielding oxindole derivatives. The intramolecular condensation may, therefore, be regarded as a function of the dissociation of the ester of sulfuric acid and the aryl amide. The significance of a coordination compound that can be dissociated in a Friedel-Crafts reaction has recently been demonstrated in a series of thorough investigations by V. V. Korshak and his associates [4,5].

The aryl amides are condensed within the organic complex ion, so that this condensation may be called an intracomplex reaction. One of the features of this reaction is its high velocity and the high yields of the reaction products. As an intramolecular reaction it will be governed by the internal structure of the organic complex ion. In the present case it is the structure of the cation with a missing electron (a positive charge) at the carbinol carbon atom (III) that is important. The substituents in the radical attached to the nitrogen atom are not linked by a conjugated chain to the central carbon atom and cannot exert any appreciable influence upon the condensation. The substituents in the phenyl radicals attached to the carbinol carbon atom will exert a strong influence. For example, when methyl groups are introduced at the para position, the last π-electrons of the benzene ring will be shifted toward the central carbon atom owing to the +I effects, resulting in a substantial decrease of the rate of condensation [6]. Groups possessing a conjugation effect will exert an even greater influence. In the carbonium ion (VIII) the positive charge is shifted to the oxygen atom (IX) as the result of conjugation in the participation of the oxygen atom of the methoxy group. But since it is (VIII) and not (IX), that enters into the reaction, the condensation rate of such aryl amides will be negligible.

Ar—NH—CO—C$^+$—⟨ ⟩—OCH$_3$ Ar—NH—CO—C=⟨ ⟩=O$^+$—CH$_3$

⇌

(VIII)   OCH$_3$ (IX)   OCH$_3$
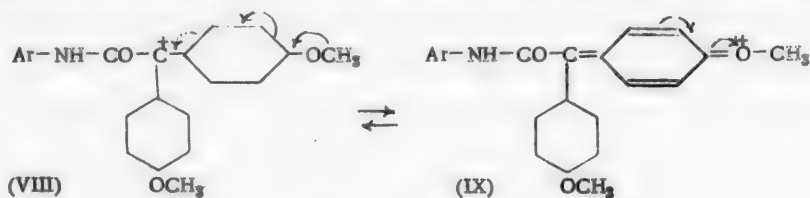
A negative charge is produced at the ortho position of the aryl amide residue (IV), due to the shift of the unshared electron pair of the nitrogen atom in the direction indicated by the arrows in (III). The charge penetrates into the electron gap of the central carbon atom, an unstable intermediate product (V) being formed, which is stabilized as the result of the evolution of a proton and the formation of the heterocyclic atom (VI). The proton combines with the SO_4H^- to form sulfuric acid (Equation 4), which re-enters the outlined circulatory process.

The mechanism proposed by us for the intramolecular condensation of aryl amides of hydroxy carboxylic acids quite satisfactorily explains the various phases of the reaction, and makes it possible to fix the limits within which the method is usable and to predict the condensation reaction.

EXPERIMENTAL

Anilide of 2,2',4,4'-tetramethoxydiphenylglycolic acid. Initial substances: 6 g (1 mole) of ethyl oxanilate, 43.5 g (5 moles) of the dimethyl ether of 4-iodoresorcinol,[1] and 4 g of magnesium. When the reaction was over, the contents of the flask were decomposed with a saturated solution of ammonium chloride, and the anilide extracted with ether. The yield of the anilide was a few per cent. The bulk of the mass did not decompose, constituting an intermediate reaction product; we had already described the formation of such products [7]. The intermediate product was treated with a 10% solution of sulfuric acid, washed with water until its reaction with Congo red was neutral, dried in the air, and then re-reacted with the organomagnesium compound. With this as our objective, we took 22.5 g of the dimethyl ether of 4-iodoresorcinol and 2.05 g of magnesium. The aggregate yield of the anilide was 1.3 g, or 18% of the theoretical. The anilide crystallized from alcohol as colorless lamellae with an m.p. of 150.5°. It dissolved in concentrated sulfuric acid, producing a blue solution. It constituted colored solutions with 0.1N solutions of sulfuric and hydrochloric acids. The colored solutions were fairly stable and were decolorized only upon heating.

A solution in acetic acid was pale yellow at ordinary temperature, but it turned red at the boiling point of the solvent. This was repeatable a large number of times. This phenomenon in chemistry is called "thermochromism" and is still without a satisfactory explanation [9].

0.2210 g substance: 6.9 ml N_2 (19°, 756 mm). 0.2001 g substance: 6 ml N_2 (19°, 756 mm). Found %: N 3.59, 3.44. $C_{24}H_{25}O_6N$. Calculated %: N 3.28.

3,3-Bis-(2,4-dimethoxyphenyl)-oxindole. 1 ml of a 10% solution of sulfuric acid was added to a solution of 0.6 g of the anilide of 2,2',4,4'-tetramethoxydiphenylglycolic acid in 7 ml of glacial acetic acid. The red coloring of the solution gradually vanished when the reaction mass was heated on a water bath (60-70°). The substance was insoluble in water or petroleum ether, though freely soluble in other organic solvents. It crystallized when its benzene solution was diluted with petroleum ether. The substance volatilized readily when heated, and was also volatile with steam. M. p. 115° (in a sealed capillary). The yield was 0.35 g, or 61.4% of the theoretical.

0.3302 g substance: 10 ml N_2 (20°, 750 mm). 0.2501 g substance: 7.8 ml N_2 (20°, 750 mm). Found %: N 3.49, 3.59. $C_{24}H_{23}O_5N$. Calculated %: N 3.46.

3,3-Diphenyloxindole. 3 ml of concentrated sulfuric acid was added to a solution of 0.7 g of the anilide of diphenyl chloroacetic acid in 10 ml of glacial acetic acid. The reaction mass was heated on a water bath (60°) 5-10 minutes until the red coloring disappeared and most of the hydrogen chloride had been eliminated. This yielded 0.6 g, or 96.7% of the theoretical. Crystallization from benzene yielded colorless prisms with an m.p. of 225°. The mixed melting point with a known sample of 3,3-diphenyloxindole exhibited no depression.

3,3-Diphenyl-4,5-benzooxindole (3,3-diphenyl-β-naphthoxindole). Initial substances: a solution of 0.5 g of the β-naphthalide of diphenylchloroacetic acid in 5 ml of glacial acetic acid and 4 g of concentrated sulfuric acid. This yielded 0.43 g, or approximately 100% of the theoretical. Colorless octahedra (from alcohol) with an m.p. of 266°. The mixed melting point with a known sample of 3,3-diphenyl-β-naphthoxindol exhibited no depression.

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[1] The dimethyl ether of 4-iodoresorcinol was prepared by the Kaufmann and Kieser method [8] and had a b.p. of 162-163° (14 mm).

SUMMARY

1. The mechanism involved in the intramolecular condensation of the N-aryl amides of hydroxy carboxylic acids is proposed and experimentally confirmed.

2. The anilide and the β-naphthalide of diphenylchloroacetic acid are used as examples to establish the ability of the aryl amides of this acid to enter into intramolecular condensation, giving rise to derivatives of oxindole.

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* See Consultants Bureau translation, p. 359.
**   Ditto   p. 1877.
***   "   p. 2343.
****   "   p. 2063.
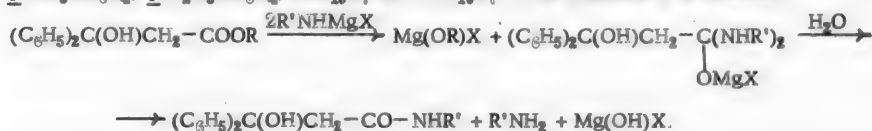*****   "   p. 1871.

THE N-ARYL AMIDES OF HYDROXY CARBOXYLIC ACIDS AND THEIR CONVERSION INTO HETEROCYCLIC COMPOUNDS

XVI. THE SYNTHESIS OF ARYL AMIDES OF β,β-DIPHENYL-β-HYDROXYPROPIONIC ACID

P. A. Petyunin and A. S. Pesis

The aryl amides of β-hydroxy carboxylic acids are compounds on which only little research has been done, only the acyl derivatives of some aryl amides of β-hydroxy carboxylic acids having been described in the literature [1]. As the result of reacting aryl oxamic and succinanilic acids with organomagnesium compounds, one of the present authors and N. G. Panferova [2,3] have developed preparative methods of synthesizing α- and γ-hydroxy carboxylic acids. An attempt to employ that reaction to synthesize the aryl amides of β-hydroxy carboxylic acids met with failure, since the malonanilic ester reacts with organomagnesium compounds in the enolic form and is recovered unchanged after the reaction mass has been decomposed. Nor did the direct reaction of the ethyl ester of β,β-diphenyl-β-hydroxypropionic acid with aromatic amines yield the desired result.

We went into the reaction of aryl halogen magnesylamines with esters in some detail in order to work out a preparative method for synthesizing the aryl amides of β-hydroxy carboxylic acids, described by Bodraux [4] in his synthesis of the aryl amides of carboxylic and phenolcarboxylic acids. Our experiments have shown that this reaction can be utilized for these purposes, yielding fully satisfactory results. We reacted the ethyl ester of β,β-diphenyl-β-hydroxypropionic acid and RNHMgX, where R = C_6H_5, o-$CH_3C_6H_4$, p-$CH_3C_6H_4$, p-$CH_3OC_6H_4$, p-$C_2H_5OC_6H_4$, α-$C_{10}H_7$ and β-$C_{10}H_7$. The reaction is as follows:

$$(C_6H_5)_2C(OH)CH_2-COOR \xrightarrow{2R'NHMgX} Mg(OR)X + (C_6H_5)_2C(OH)CH_2-\underset{\underset{OMgX}{|}}{C}(NHR')_2 \xrightarrow{H_2O}$$

$$\longrightarrow (C_6H_5)_2C(OH)CH_2-CO-NHR' + R'NH_2 + Mg(OH)X.$$

The properties of the synthesized aryl amides of β,β-diphenyl-β-hydroxypropionic acid are given in the table.

| No.	Formula of aryl amide	M.p.
1	$(C_6H_5)_2C(OH)CH_2CONHC_6H_5$..........	166.5°
2	$(C_6H_5)_2C(OH)CH_2CONHC_6H_4CH_3$-p...	155-156
3	$(C_6H_5)_2C(OH)CH_2CONHC_6H_4CH_3$-o...	167
4	$(C_6H_5)_2C(OH)CH_2CONHC_6H_4OCH_3$-p..	160
5	$(C_6H_5)_2C(OH)CH_2CONHC_6H_4OC_2H_5$-p.	166
6	$(C_6H_5)_2C(OH)CH_2CONHC_{10}H_7$-$\alpha$........	186
7	$(C_6H_5)_2C(OH)CH_2CONHC_{10}H_7$-β.......	188.5

EXPERIMENTAL

Anilide of β,β-diphenyl-β-hydroxypropionic acid. A solution of 9.8 g (3 moles) of freshly distilled aniline in 30 ml of ether was added to bromomethylmagnesium, prepared from 13 g (3 moles of ethyl bromide and 2.88 g of magnesium in 30 ml of ether. A solution of 10.8 g (1 mole) of the ethyl ester of β,β-diphenyl-β-hydroxypropionic acid [*] in 30 ml of ether was added to the resulting suspension or solution of phenylbromomagnesylamine. Finally, the contents of the flask were boiled on a water bath for 1.5-2 hours.

After the reaction mass had been decomposed with dilute hydrochloric acid, the precipitate was filtered out, washed on the filter with water until its acid reaction with Congo red had disappeared, and air-dried. Driving off the ether yielded some more of the substance. The anilide was insoluble in water, slightly soluble in ether, and freely soluble in acetone and chloroform. When reacted with conc. sulfuric acid it turns the acid yellow, the color gradually changing to green. Crystallization from alcohol yielded colorless needles with a m.p. of 166.5°. The yield was 6 g, or 47.3% of the theoretical.

[*] The ethyl ester of β,β-diphenyl-β-hydroxypropionic acid was prepared by a S.N.Reformatsky reaction [5]; its yield was 60% of the theoretical and its m.p. 84° [6].

When we hydrogenated the steroid ketone (II) with a Pd catalyst in dioxane, we obtained the saturated compound (III), its oxidation with potassium permanganate yielding the sulfone (IV):

(II) (III) (IV)
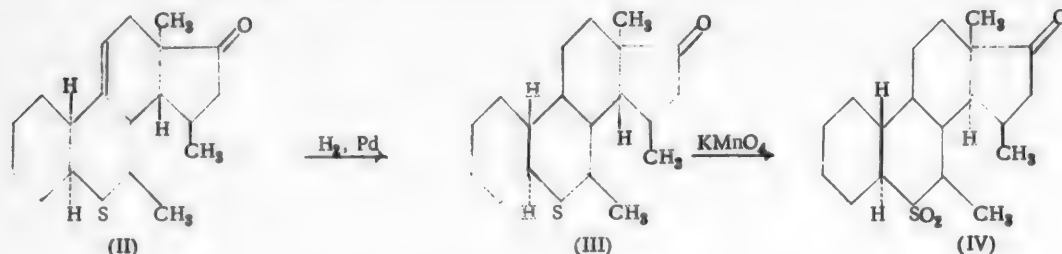
It is worthy of note that the unsaturated condensation product (II) does not form a semicarbazone of 2,4-dinitrophenylhydrazone even when heated for a long time with the respective reagents, whereas the hydrogenated compounds (III) and (IV) form 2,4-dinitrophenylhydrazones fairly readily.

EXPERIMENTAL

The initial diene (I) was prepared by splitting water from the respective vinyl alcohol by means of p-toluenesulfonic acid or potassium bisulfate [1].

Condensation of the diene (I) with 1,3-dimethyl-Δ^1-cyclopenten-5-one. 1.8 g of the diene (I) (b.p. 128-129° at 11 mm; n_D^{20} 1.5430) was dissolved in 33 g of dimethylcyclopentenone (b.p. 164-166°; n_D^{20} 1.4600 [3], 0.04 g of pyrogallol was added, and the solution was heated to 200° for 5 hours in an atmosphere of dry nitrogen within a steel ampoule. The dimethylcyclopentenone was driven off in vacuo, after which 0.8 g of the initial diene (b.p. 110-120° at 8 mm; n_D^{20} 1.5290) was driven off. When the tarry residue was processed with methanol we obtained 0.25 g of crude crystals. Recrystallization from petroleum ether yielded 0.11 g of the condensation product (IIa) or (IIb) with a m.p. of 142°.

5.130 mg substance: 14.060 mg CO_2; 4.210 mg H_2O; 1.585 mg SO_4.* 5.290 mg substance: 14.520 mg CO_2; 4.470 mg H_2O; 1.670 mg SO_4. Found %: C 74.80, 74.91; H 9.18, 9.45; S 10.31, 10.53. $C_{19}H_{28}OS$. Calculated %: C 74.95; H 9.27; S 10.52.

0.1 g of the condensation product was refluxed for 20 hours in methanol with 0.042 g of semicarbazide acetate. When the solution cooled, crystals with a m.p. of 142° settled out. Their mixed melting point with the initial substance exhibited no depression.

A hydrochloric acid solution of 0.11 g of the condensation product, 0.07 g of 2,4-dinitrophenylhydrazone, and 0.07 g of hydrochloric acid was boiled for 5 hours, the condensation product again being recovered unchanged.

Hydrogenation of the steroid ketone (II). 0.29 g of the condensation product (II) (b.p. 142°) was hydrogenated with 0.3 g of a Pd catalyst (PdO on $CaCO_3$) in a solution of 18 ml of absolute dioxane. 16 ml of hydrogen was absorbed in 7 hours after which hydrogenation ceased. Another 0.3 g of the Pd catalyst was added, and hydrogenation was continued at 100°. Another 9 ml of hydrogen was absorbed, after which hydrogenation ceased. A total of 25 ml of hydrogen (25°, 737 mm) was absorbed. The solution was filtered, and the dioxane was driven off. This yielded 0.23 g of a saturated steroid ketone (III) with a m.p. of 135.5-136° (from petroleum ether). The mixed melting point with the initial substance (II) was 116-128°.

4.891 mg substance: 13.160 mg CO_2; 3.930 mg H_2O; 1.480 mg SO_4. 5.110 mg substance: 13.660 mg CO_2; 4.210 mg H_2O; 1.550 mg SO_4. Found %: C 73.43, 72.95; H 8.99, 9.22; S 10.10, 10.13. $C_{19}H_{30}OS$. Calculated %: C 74.44; H 9.86; S 10.46.

The 2,4-dinitrophenylhydrazone of the steroid ketone (III) was prepared by boiling an alcoholic solution of the substance with 2,4-dinitrophenylhydrazine hydrochloride for an hour; its m.p. was 220-222° (from alcohol).

2.350 mg substance: 0.254 ml N_2 (23°, 752 mm). Found %: N 12.33. $C_{25}H_{34}O_4N_4S$. Calculated %: N 11.51.

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* The substance was simultaneously analyzed for C, H, and S by the Korshun and Shevelova method [4].

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Oxidizing the steroid ketone (III). 0.15 g of the substance (III) was dissolved in 10 ml of acetone and 0.38 ml of 10% sulfuric acid was added to the solution, which was then cooled with ice water and agitated while 0.1 g of potassium permanganate was added. The precipitated manganese dioxide was filtered out and washed with acetone. After the acetone had been driven off, the residue was found to consist of crystals of the sulfone (IV), whose m.p. was 186-186.5° (from alcohol).

4.550 mg substance: 11.270 mg CO_2; 3.450 mg H_2O; 1.250 mg SO_4. 4.010 mg substance: 9.910 mg CO_2; 3.100 mg H_2O; 1.150 mg SO_4. Found %: C 67.60; 67.44; H 8.48, 8.65; S 9.17, 9.57. $C_{19}H_{30}O_3S$. Calculated %: C 67.41; H 8.93; S 9.47.

The 2,4-dinitrophenylhydrazone of the sulfone (IV) was partially formed when an alcoholic solution of the sulfone (IV) was reacted with 2,4-dinitrophenylhydrazine hydrochloride in the cold. When an alcoholic solution of 35 mg of the sulfone (IV) and 24 mg of 2,4-dinitrophenylhydrazine was heated, we obtained the 2,4-dinitrophenyl-hydrazone with a m.p. of 265-266° (from a mixture of benzene and petroleum ether).

SUMMARY

1. A diene condensation has been employed in synthesizing for the first time the sulfur analogs of the steroid (IIa) or (IIb), which contain sulfur in the ring B.

2. In the synthesized compound the A and B rings are linked together in the trans position, the rings C and D being linked in the cis position.

3. The product of the diene synthesis (II) does not yield the usual derivatives at the carbonyl group, though the hydrogenated products (III) and (IV) readily yield 2,4-dinitrophenylhydrazones.

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*See Consultants Bureau translation, p. a-637.

# DERIVATIVES OF ACETYLENE

141. HETEROCYCLIC COMPOUNDS

### XVII. THE STRUCTURE OF TETRAHYDRO-γ-THIOPYRONES AND THE MECHANISM OF THEIR FORMATION.

KIZHNER REDUCTION OF TETRAHYDRO-γ-THIOPYRONES

I.N.Nazarov, I.A.Gurvich, and A.I.Kuznetsova

In one of our preceding reports we described a new and simple method of synthesizing various tetrahydro-γ-thiopyrones by reacting allyl vinyl ketones with hydrogen sulfide:

R and R' = hydrogen or an alkyl group
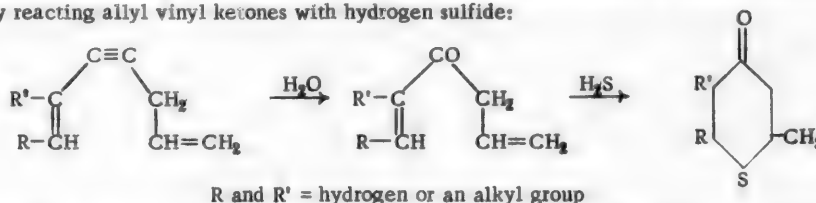
We decided to reduce 2-methyltetrahydro-1-thiopyran-4-one (I) to the known a-methylpentamethylene sulfide (II), obtained by a Grishkevich-Trokhimovsky reaction of sodium sulfide with 1,5-dibromohexane, about whose six-membered ring structure there is no doubt [2], in order to establish the structure of the tetrahydro-γ-thiopyrones we had synthesized:

(I)   (II)
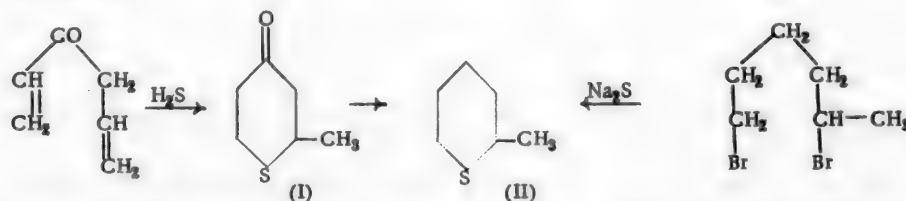
The Clemmensen method has been employed in most of the known instances of the reduction of tetrahydro-γ-thiopyrones to tetrahydrothiopyrans. This was the method used to reduce 2,6-diphenyltetrahydro-1,4-thiopyrone [3], 2,2,6,6-tetramethyltetrahydro-1,4-thiopyrone [4], as well as several thiochromanones [5], thiophene ketones [6], and homothiochromanone [7] to the respective thiopyrans.

Instances are also known, however, of the reduction of aldehydes and ketones of the thiophene [8] and thioxanthone [9] series by the Kizhner method. This method has also been utilized in reducing the dimer of acrolein, which is an aldehyde of the pyran series [10]. We tried to reduce 2-methyltetrahydro-1-thiopyran-4-one (I) by the Clemmensen method, using alcohol as the solvent, but the main result we secured was rupture of the ring.

Then we resorted to the Kizhner method to reduce the tetrahydro-γ-thiopyrones. The reaction was carried out in ethylene glycol without precipitating a hydrazone. Reducing 2-methyltetrahydro-1-thiopyran-4-one (I) by the Kizhner method yielded 2-methyltetrahydrothiopyran (II), the yield being 62%. The constants of the synthesized thiopyran (II), the melting point of the corresponding sulfone, and the sublimation point of its methiodide, all agreed with the constants for a-methylpentamethylene sulfide given in the literature [2]. We have therefore shown that the cyclic sulfur-containing ketone synthesized by reacting allyl vinyl ketone with hydrogen sulfide actually has a six-membered ring structure.

When we reduced 2,5-dimethyltetrahydro-1-thiopyran-4-one (III) by the Kizhner method, we secured a 61% yield of 2,5-dimethyltetrahydrothiopyran (IV), oxidation of which with potassium permanganate yielded a liquid

sulfone. The crystalline derivatives of the thiopyran (IV) with methyl iodide and mercuric chloride were likewise obtained:
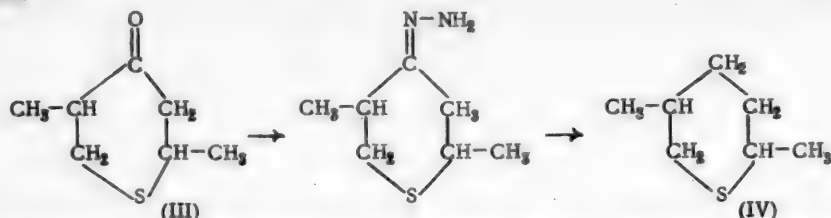
The formation of a six-membered thiopyran ring when allyl vinyl ketones are acted upon by hydrogen sulfide has also been demonstrated in bicyclic systems.

The product of the diene condensation of 2-methylthiopyrone dioxide with butadiene yields the sulfone (VI) upon reduction in an acid medium; this sulfone was previously obtained by reacting hydrogen sulfide with allyl Δ^1-cyclohexenyl ketone, followed by oxidizing the resultant thiochromanone (V):
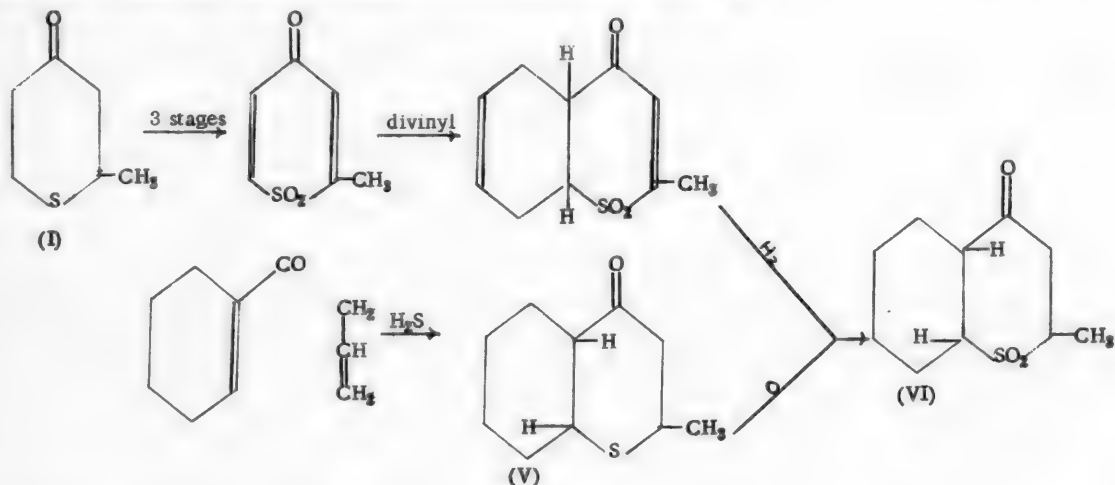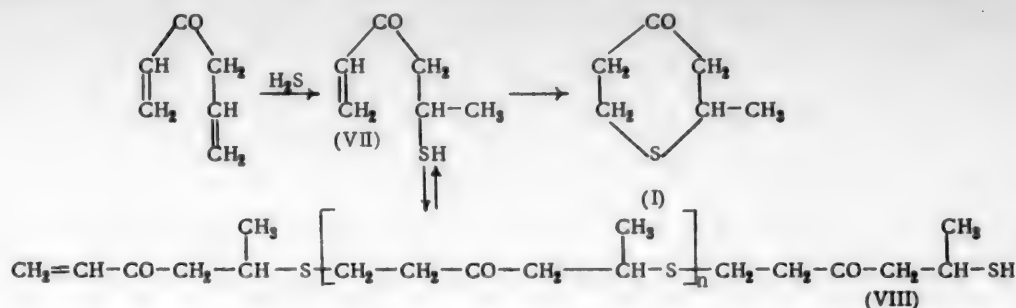

The six-membered structure of the thiopyrone (I) thus leads to a six-membered structure for the sulfur-containing ring of the hexahydrothiochromanone (V).

These findings, together with the conversion of several tetrahydro-γ-thiopyrones into thiopyrone dioxides that we have carried out recently and the behavior of the latter in a diene synthesis incontrovertibly prove the six-membered structure of the sulfur-containing heterocyclic compounds we have synthesized by adding hydrogen sulfide to allyl vinyl ketones and divinyl ketones.

As we had established previously [1], the yield of tetrahydro-γ-thiopyrones is as high as 70% when allyl vinyl ketones are reacted with hydrogen sulfide. The yield of 2-methyltetrahydro-1-thiopyran-4-one (I) was only 30%, however. The reason for so low a yield in this instance was the formation of large quantities of a polymer of the unsaturated ketone (VII). We found that formation of the polymer promoted an interruption of the reaction between the stage in which the ketothiol was formed and that in which it was cyclized. By effecting cyclization as soon as the ketothiol had been synthesized we secured a 65% yield of the 2-methyltetrahydrothiopyrone (I).

Analysis of the polymer indicated that it was the trimer of the unsaturated ketothiol (VII). The polymer exhibited the qualitative reactions for the sulfhydryl group with nitrous acid and sodium nitroprusside. When the polymer (VIII) was boiled with a dilute solution of an alcoholic alkali, it was partially cleaved, yielding the ketothiol (VII) and then cyclizing it to the thiopyrone (I), which we found in the reaction products. We had previously observed this sort of cleavage of a sulfide when it was boiled in dilute alcoholic solutions of an alkali [11]: it pointed to the presence of sulfide bonds in the polymer (VIII). Our results enable us to picture the reaction involved in the formation of 2-methyltetrahydro-1-thiopyran-4-one as follows:

$$\text{(VII)} \quad \xrightarrow{H_2S} \quad \text{(I)}$$

$$CH_2=CH-CO-CH_2-\underset{CH_3}{CH}-S\left[CH_2-CH_2-CO-CH_2-\underset{CH_3}{CH}-S\right]_n CH_2-CH_2-CO-CH_2-\underset{CH_3}{CH}-SH$$
$$\text{(VIII)}$$

The first stage of the addition of hydrogen sulfide to an allyl vinyl ketone is the formation of the unsaturated ketothiol (VII), which is readily cyclized to 2-methyltetrahydro-1-thiopyran-4-one (I) by heating it with sodium acetate and is polymerized in the cold to the product (VIII).

As Nazarov and Kuznetsova had shown previously [12], β,β-dimethyl divinyl ketone behaves similarly in a reaction with hydrogen sulfide. This yields an unsaturated ketothiol (IX), which is cyclized to 2,2-dimethyltetrahydro-1,4-thiopyrone (X) when heated with sodium acetate and is converted to the corresponding polymer when stored.

$$\text{(IX)} \qquad \xrightarrow{H_2S} \qquad \text{(X)}$$
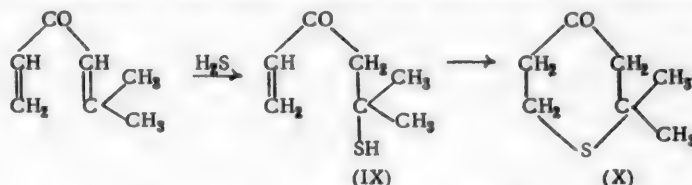
This is not the only possible way of producing tetrahydro-γ-thiopyrones from unsaturated ketones, however. As we know, allyl isopropenyl ketone can add two molecules of hydrogen sulfide under these conditions, the resultant ketodithiol (XI) being stable in the cold, though it is readily cyclized when heated in an alkaline medium, giving off hydrogen sulfide:

$$\text{(XI)} \qquad \xrightarrow{H_2S} \qquad \text{(III)} \quad + H_2S$$
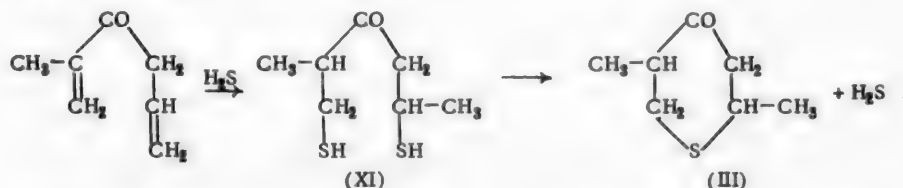
2-Methyltetrahydro-1-thiopyran-4-one (I). a) 10 g of anhydrous sodium acetate was dissolved in 200 ml of 96% alcohol, the flask was immersed in ice water, and hydrogen sulfide was passed through the solution for 30 minutes. Then 12 g of vinyl allyl ketone (b.p. 60-62° at 28 mm; n_D^{20} 1.4690) [13] was added to the solution in the course of 20 minutes, with continuous stirring and the hydrogen sulfide passing through the solution continuously [13]. Hydrogen sulfide was passed through for 30 more minutes after the vinyl allyl ketone had been added, and then the solution was refluxed for 5 hours. The mercaptan odor disappeared. The alcohol was driven off on a water bath, 30 ml of water was added, and the product was extracted with ether, washed with water, dried with sodium sulfate, and distilled in vacuo. This yielded 10.5 g of the previously described [1] 2-methyltetrahydro-1-thiopyran-4-one (I), with a b.p. of 84-85° at 13 mm, n_D^{20} 1.5090, representing 65% of the theoretical yield.

b) 6 g of anhydrous sodium acetate was dissolved in 200 ml of alcohol, and the solution was saturated with hydrogen sulfide at 0°. The solution was continuously stirred for one hour with uninterrupted passage of the hydrogen sulfide while 25.5 g of vinyl allyl ketone was added. Then hydrogen sulfide was passed through for another 4 hours, and the solution was allowed to stand overnight. A transparent, viscous layer of resin formed on the bottom of the flask. Another 200 ml of alcohol and 4 g of sodium acetate were added, and the solution was boiled for 8 hours. After the solution had cooled, it was decanted from the resin and processed as described in the preceding experiment. This yielded 5.4 g of 2-methyltetrahydrothiopyrone (I), b.p. 70.5-72° at 8.5 mm; n_D^{19} 1.5094. 12 g of a polymerized residue, which decomposed when heated, was left in the distilling flask. The transparent resin secured after the solution had been boiled was washed with water and acetone, filtered, and dried over phosphoric anhydride in a vacuum desiccator. The resultant viscous, transparent resin was sparingly soluble in the usual solvents, exhibited a

qualitative reaction for the sulfhydryl group with nitric acid (green coloration) and sodium nitroprusside (crimson coloration), and was a polymer of the unsaturated ketothiol (VII), with triple its molecular weight:

0.1196 g substance: 17.00 g dioxane: Δt 0.082°. 0.1600 g substance; 16.25 g dioxane: Δt 0.112°. 4.220 mg substance: 8.625 mg CO_2; 3.050 mg H_2O; 2.970 mg SO_4. 4.095 mg substance: 8.378 mg CO_2; 2.990 mg H_2O; 2.861 mg SO_4. Found %: C 55.77, 55.83; H 8.08, 8.17; S 23.46, 23.42. M 394.6, 404.3. $(C_6H_{10}OS)_3$. Calculated %: C 55.35; H 7.74; S 24.63. M 390.6.

Cleavage of the polymer of (VII). 4 g of the polymer (VIII) of the unsaturated ketothiol was refluxed for 8 hours with 40 ml of alcohol that contained 0.08 g of potassium hydroxide (0.2% of the solution). When the alcoholic solution had cooled, it was decanted from the resin, the alcohol was driven off, and the residue was treated in the customary manner. Distillation yielded 0.7 g of 2-methyltetrahydrothiopyran-4-one (I), b.p. 88-89° at 14.5 mm; n_D^{23} 1.5060.

2-Methyltetrahydrothiopyran (II). (a-Methylpentamethylene sulfide). 6.5 g of 2-methyltetrahydro-1-thiopyran-4-one (I) (b.p. 59-60° at 6 mm; n_D^{20} 1.5094), 40 ml of ethylene glycol, and 10 ml of hydrazine hydrate were placed in a three-necked round-bottomed flask, fitted with a thermometer immersed in the liquid and a descending condenser. The solution was heated to 130-160°, about 5 ml of a cloudy liquid being driven off. Then the solution was cooled to 40°, and 6 g of fused potassium hydroxide was added. The descending condenser was replaced by a reflux condenser and the flask was heated on a metallic bath at 140-170° (125-142° within the liquid) for 6 hours until no more nitrogen was evolved. The 2-methyltetrahydrothiopyran (II) was distilled from the reaction mixture, and the distillate was extracted with ether. The ether extract was dried with calcium chloride, and the product was fractionated at atmospheric pressure. This yielded 3.6 g of a colorless, volatile liquid, b.p. 150-152.5°, constituting 62% of the theoretical yield. After the substance had been distilled over sodium, its constants were as follows: b.p. 150.5-151.5° at 755 mm; n_D^{20} 1.4902; $n_D^{18.5}$ 1.4910; d_4^{20} 0.9406; $d_4^{18.5}$ 0.9438; MR 35.73, 35.66; calc. 35.68.

5.910 mg substance: 13.435 mg CO_2; 5.527 mg H_2O; 4.870 mg SO_4. 6.348 mg substance: 14.463 mg CO_2; 5.970 mg H_2O; 5.215 mg SO_4. 4.662 mg substance: 10.590 mg CO_2; 4.333 mg H_2O. Found %: C 62.04, 62.17, 61.99; H 10.46, 10.52, 10.40; S 27.50, 27.42. $C_6H_{12}S$. Calculated %: C 62.04; H 10.41; S 27.58.

Methiodide of 2-methyltetrahydrothiopyran. 0.4 g of 2-methyltetrahydrothiopyran (II) and 0.6 g of methyl iodide were poured into a flask with a ground-glass stopper. A week later elongated needles of the methiodide were filtered out. The methiodide was recrystallized twice from a mixture of acetone and ether, after which it sublimed at 158-159° without melting.

3.450 mg substance: 1.335 ml 0.02 N I_2. Found %: S 12.40. $C_6H_{12}S \cdot CH_3I$. Calculated %: S 12.42.

Compound of 2-methyltetrahydrothiopyran with mercuric chloride. Alcoholic solutions of 0.4 g of 2-methyltetrahydrothiopyran (II) and of 0.95 g of mercuric chloride were poured together, an abundant crystalline precipitate being thrown down at once. Double recrystallization from alcohol yielded minute needles, m.p. 102-102.5°.

6.030 mg substance: 1.536 ml 0.02 N I_2. 4.390 mg substance: 1.145 ml 0.02 N I_2. Found %: S 8.16, 8.17. $C_6H_{12}S \cdot HgCl_2$. Calculated %: S 8.27.

2-Methyltetrahydrothiopyran dioxide. 1 g of 2-methyltetrahydrothiopyran (II) was dissolved in 60 ml of acetone, and the solution was stirred continuously and water-cooled while 6.1 ml of 10% sulfuric acid and 2.2 g of powdered potassium permanganate were added to it during the course of 30 minutes. Stirring was continued for another hour. Then the manganese dioxide was filtered out and washed several times with acetone. Driving off the solvent in vacuo left a residue of 1 g of a crystalline sulfone. Three recrystallizations from a mixture of ether and petroleum ether yielded elongated needles, m.p. 68-68.5°.

4.212 mg subtance: 7.505 mg CO_2; 3.083 mg H_2O; 2.770 mg SO_4. 5.640 mg substance: 10.042 mg CO_2; 4.133 mg H_2O; 3.650 mg SO_4. Found %: C 48.63, 48.64; H 8.19, 8.20; S 21.95, 21.60. $C_6H_{12}O_2S$. Calculated %: C 48.60; H 8.15; S 21.62.

Data in the literature [2] for a-methylpentamethylene sulfide: b.p. 151.4-151.6° at 750 mm (corr); $d_4^{18.5}$ 0.9449; $n_D^{18.5}$ 1.4884; subliming point of the methiodide: 158-159°; melting point of the mercuric chloride compound: 97-98°; melting point of a-methylpentamethylene sulfone: 68-68.5°.

2,5-Dimethyltetrahydrothiopyran (IV). 7.2 g of the previously described tetrahydro-1-thiopyran-4-one (III) [1] (m.p. 71°), 40 ml of ethylene glycol, and 10 ml of hydrazine hydrate were heated together to 130-160° as described in the preceding experiment 6 ml of a cloudy liquid being distilled off in the course of 30 minutes. Then the solution was cooled, and 5 g of fused potassium hydroxide was added to it. The reaction mixture was refluxed, nitrogen beginning to evolve when the temperature of the liquid reached 125°. Heating was continued for 5 hours

at a solution temperature of 143-147° (bath temperature 162-167°) until no more nitrogen was given off. Then the 2,5-dimethyltetrahydrothiopyran (IV) was distilled from the reaction mixture, the distillate being extracted with ether, and the ether extract dried with calcium chloride. Fractionation yielded 4 g of a volatile colorless liquid, or 61% of the theoretical yield; b.p. 162-164°. The constants of the 2,5-dimethyltetrahydrothiopyran (IV) were as follows after distillation over sodium:

B.p. 163-163.5°; n_D^{20} 1.4850; d_4^{20} 0.9230; MR 40.43; calculated 40.30.

4.872 mg substance: 11.512 mg CO_2; 4.725 mg H_2O; 3.570 mg SO_4. 4.420 mg substance: 10.420 mg CO_2; 4.250 mg H_2O; 3.240 mg SO_4. 4.628 mg substance: 10.947 mg CO_2; 4.500 mg H_2O. Found %: C 64.48, 64.34, 64.55; H 10.84, 10.76, 10.88; S 24.46, 24.47. $C_7H_{14}S$. Calculated %: C 64.59; H 10.83; S 24.62.

Methiodide of 2,5-dimethyltetrahydrothiopyran. 0.34 g of 2,5-dimethyltetrahydrothiopyran and 0.7 g of methyl iodide were poured together in a flask with a ground-glass stopper. After a week had elapsed, the resulting crystals were filtered out and recrystallized from acetone. The methiodide of 2,5-dimethyltetrahydrothiopyran consists of colorless needles that sublime at 141-142°.

3.050 mg substance: 1.157 ml 0.02 N I_2. Found %: S 12.15. $C_7H_{14}S \cdot CH_3I$. Calculated %: S 11.78.

Mercuric chloride compound of 2,5-dimethyltetrahydrothiopyran. Alcoholic solutions of 0.4 g of 2,5-dimethyltetrahydrothiopyran and of 0.95 g of mercuric chloride were poured together. An abundant crystalline precipitate was thrown down at once. Double recrystallization from alcohol yielded minute needles with a m.p. of 121-121.5°.

5.650 mg substance: 1.343 ml 0.02 N I_2. 5.430 mg substance: 1.322 ml 0.02 N I_2. Found %: S 7.61, 7.80. $C_7H_{14}S \cdot HgCl_2$. Calculated %: S 7.98.

SUMMARY

1. It has been demonstrated that the sulfur heterocyclic compounds produced by the action of hydrogen sulfide upon vinyl allyl ketones have a six-membered ring.

2. Kizhner reductions of the tetrahydro- γ -thiopyrones yielded 60% of the respective tetrahydrothiopyrans.

3. The yield of 2-methyltetrahydro-1-thiopyran-4-one (I) has been improved, and a suggestion is made concerning the mechanism involved in its formation.

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# DERIVATIVES OF ACETYLENE

142. HETEROCYCLIC COMPOUNDS

XVIII. DIENE SYNTHESIS BASED UPON DIOXIDES OF

DISUBSTITUTION DERIVATIVES OF γ-THIOPYRONES

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In our previous researches we started out with tetrahydro- γ-thiopyrones and prepared sulfur-containing cyclic dienes, which were used in diene syntheses to secure polycyclic sulfur compounds [1,2]:
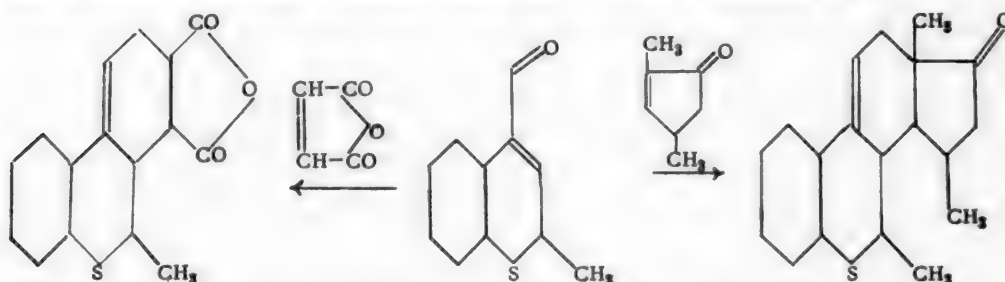

Another possible way of constructing sulfur-containing polycyclic compounds based on tetrahydro- γ-thiopyrones consisted of preparing thiopyrone dioxides and using them as the olefin constituents in a diene synthesis:
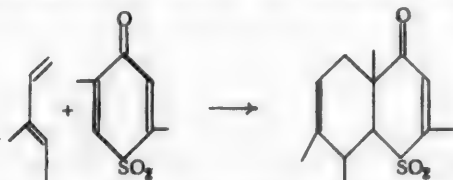

In our present research we have secured several dioxides of substitution derivatives of the γ-thiopyrones and investigated their condensation with butadiene; this yielded compounds with an angular methyl group.

The usual method of preparing dioxides of the γ-thiopyrones involves the bromination of the dioxides of the tetrahydro- γ-thiopyrones, followed by splitting off hydrogen bromide:
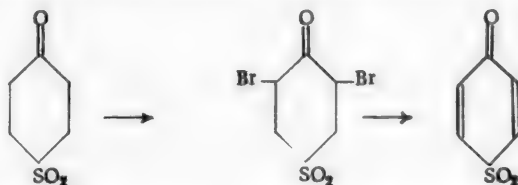
This method was used to secure the dioxides of thiopyrone and dihydrothiopyrone [3,4], 2,6-dimethylthiopyrone [5], 2,6-diphenylthiopyrone [6], and of various thiochromones [7]. We used this method to secure several new dioxides of substitution derivatives of γ-thiopyrones from the dioxides of various tetrahydro- γ-thiopyrones previously described by us [8].

(I) (II) (III) (IV) (V) (VI)
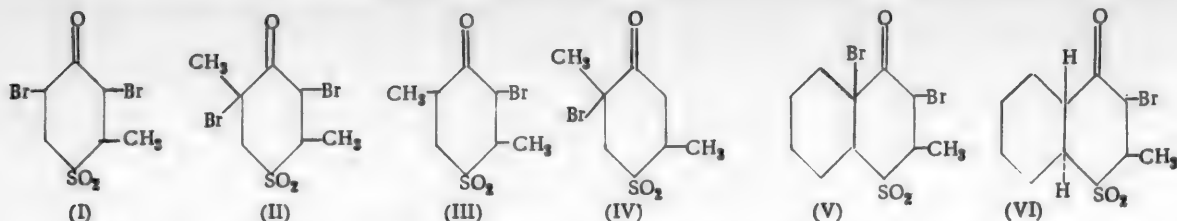
When two molecules of bromine were heated with a solution of 2-methyltetrahydro-1-thiopyran-4-one in glacial acetic acid, we obtained the corresponding cyclic dibromoketosulfone (I), the yield being 86%. A quantitative yield of the cyclic dibromoketosulfone (II) was similarly prepared from the dioxide of 2,5-dimethyltetrahydro-1-thiopyran-4-one. The action of one molecule of bromine upon 2,5-tetrahydro-1-thiopyran-4-one under the same conditions yielded a mixture of the isomeric monobromoketosulfones (III) and (IV), the yield being 88%. When one molecule of bromine was reacted with a solution of 2,5-dimethyltetrahydro-1-thiopyran-4-one at room temperature, with hydrogen bromide present as a catalyst, we secured a mixture of the monobromides (III) and (IV), with a lower yield, though the product that predominated in this latter mixture was the tertiary monobromoketosulfone (IV).

Bromination of the dioxide of trans-2-methylhexahydro-1-thiochroman-4-one with two molecules or one molecule of bromine yielded, respectively, the bicyclic dibromosulfone (V), the yield being 91%, and the monobromosulfone (VI), the yield being 60%, both belonging to the trans series of compounds.

All the cyclic bromoketosulfones (I-VI) we have synthesized are colorless crystalline substances that are stable in the pure state when kept for a long time.

Splitting hydrogen bromine from the bromoketosulfones (I-VI) by means of sodium acetate in boiling acetone produced dioxides of the γ-thiopyrones (VII-XII), the yields ranging from 70 to 80%:


(VII) (VIII) (IX) (X) (XI) (XII)
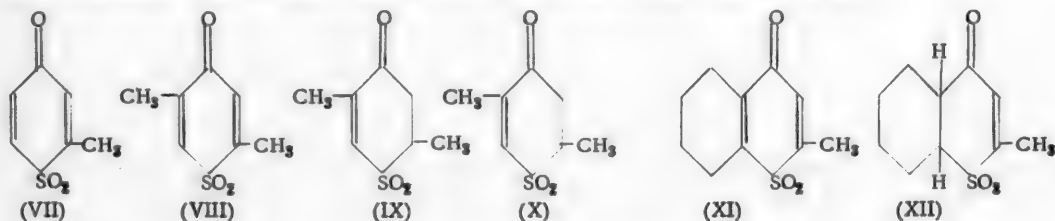
The bicyclic sulfone (XII), produced by splitting hydrogen bromide out of the bromosulfone (VI), has a trans configuration.

The properties of the synthesized dioxides of the γ-thiopyrones resemble those of the 1,4-benzoquinones. The sulfones (VII-X) cause sneezing. The sulfones (VII), (VIII), and (XI) have a lemon-yellow color. The sulfones (VII) and (VIII) stain the skin yellow. The oxime of the sulfone (VIII) is also a colored compound.

We know that unsaturated α,β-sulfones enter into condensation with 1,3-dienes like the unsaturated α,β-ketones [9].

The dioxide of 1,4-thiopyrone [4] reacts with butadiene extremely readily, resembling quinone in this respect. The dioxides of the substituted γ-thiopyrones we synthesized (VII-IX) likewise condense readily with butadiene, though the temperatures required are higher. When the sulfone (VII) is dissolved in dioxane and heated to 150° for 4-5 hours in a steel ampoule together with an excess of divinyl, we get cis-2-methyl-5,8,9,10-tetrahydro-1-thiochromen-4-one (XIII), the yield being 92%:


(VII) 150° (XIII)
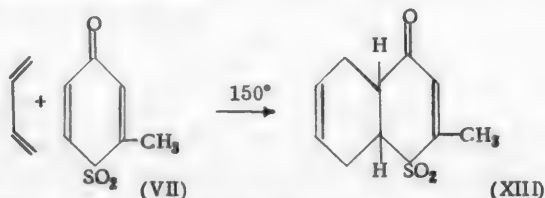
Raising the temperature to 200° does not affect this result: the condensation products exhibit no signs of thioxanthone derivatives, which might have been produced by the addition of two molecules of divinyl to the sulfone (VII).

The sulfone (VIII) condenses with butadiene at 200°, producing a yield of 61% of the dioxide of cis-2,10-dimethyl-5,8,9,10-tetrahydro-1-thiochromen-4-one (XIV). At 150° a large part of the initial sulfone (VIII) is recovered from the reaction:

$$CH_3 \quad + \quad \xrightarrow{200°} \quad (VIII) \longrightarrow (XIV)$$

(VIII)   (XIV)
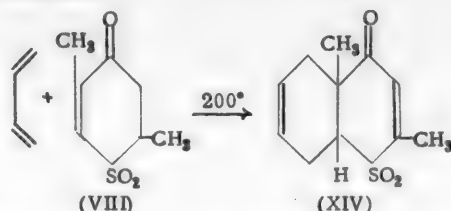
The sulfone (IX) also reacts with butadiene at 200°, producing two stereoisomeric dioxides of cis-2,10-dimethyl-5,8,9,10-tetrahydro-1-thiochroman-4-one (XV), the overall yield being 65%:

$$\xrightarrow{200°}$$

(IX)   (XVa)   (XVb)
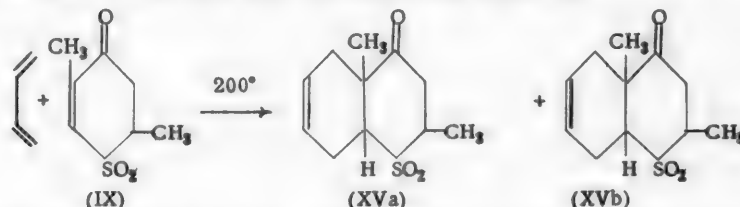
At 150° the sulfone (IX) does not react with divinyl, being recovered from the reaction unchanged. The sulfone (X) does not react with butadiene at all, even at 200°.

These results may be compared with the findings on the condensation of butadiene with substitution derivatives of the quinones. Though benzoquinone itself can be readily condensed with two molecules of butadiene [10], 2-methyl-1,4-benzoquinone reacts with only one molecule of butadiene at temperatures up to 110°, while in the case of 2,5-dimethyl-1,4-benzoquinone, which does enter into condensation with two molecules of butadiene at temperatures in excess of 100°, the condensation product containing one molecule of butadiene predominates [12].

Thus, the presence of substituents in thiopyrone dioxides hampers their condensation with butadiene, as in the case of the quinones. Our findings indicate that the position of the substituent in the thiopyrone ring is of major importance for the diene condensation. The inability of the sulfone (XIII), or of the similarly constructed sulfone (XIV), to enter into diene synthesis with a second molecule of butadiene is due to the presence of a substituent at the 2 position. This assumption is borne out by the fact that one of the dihydrothiopyrone dioxides (X) also fails to enter into diene synthesis at 200°, whereas the dioxides (VIII) and (IX), which are substituted at the 5 position, react with butadiene readily at 200°.

Hence, the presence of methyl groups at the a-position to the ketone group merely hampers the reaction, while the presence of substituents at the a-position to the sulfone group renders the condensation of thiopyrone dioxides with butadiene impossible, even at 200°.

EXPERIMENTAL

The initial sulfones were prepared by oxidizing tetrahydro-γ-thiopyrones with potassium permanganate in acetone [8].

I. Bromination of Dioxides of Tetrahydro-γ-thiopyrones

Dioxide of 3,5-dibromo-2-methyltetrahydro-1-thiopyran-4-one (I). 4.4 g of 2-methyltetrahydro-1-thiopyran-4-one dioxide (m.p 79-80°) and 50 ml of glacial acetic acid were placed in a three-necked round-bottomed flask, then 4.1 g of bromine was poured into the resulting solution. The solution was heated to 65-67° on a water bath with vigorous stirring. At that temperature the solution was decolorized instantaneously. The bath was taken away, and another 4 g of bromine was added. As the solution cooled, 6 g of the dibromide settled out, while another 1.5 g of the dibromide settled out when part of the acetic acid was driven off in vacuo (30-40 mm). The product totaled 7.5 g, or 86% of the theoretical yield. The dibromoketosulfone (I) consisted of colorless crystals with a m.p. of 219-219.5° (from acetic acid).

2.860 mg substance: 2.355 mg CO_2; 0.610 mg H_2O. 5.911 mg substance: 4.895 mg CO_2; 1.355 mg H_2O; 4.745 mg $SO_4 + Br^-$. Found %: C 22.47, 22.60; H 2.38, 2.57; S 10.13; Br 50.26. $C_6H_8O_3SBr_2$. Calculated %: C 22.52; H 2.53; S 10.02; Br 49.94.

Dioxide of 3,5-dibromo-2,5-dimethyltetrahydro-1-thiopyran-4-one (II). 10 g of 2,5-dimethyltetrahydro-1-thiopyran-4-one dioxide (m.p.138°) was dissolved in 80 ml of glacial acetic acid. The solution was heated to 65° and vigorously stirred while 18 g of bromine in 20 ml of glacial acetic acid was added to it a drop at a time during the course of 2 hours. (Each drop was added only after the solution had been decolorized again). Then the solution was allowed to stand overnight. The next day 12 g of the dibromide was filtered out, another 3.1 g of the dibromide settling out after part of the acetic acid had been driven off in vacuo at 50 mm. Driving off all the solvent yielded another 3.5 g of the dibromide in the residue. Thus the dibromide (II) produced totaled 18.6 g, which was nearly the quantitative yield. The dibromoketosulfone (II) consisted of colorless crystals with a m.p. of 184.5-185° (from acetone).

31.621 mg substance: 0.9411 ml 0.02 N $AgNO_3$. 22.830 mg substance: 0.6802 ml 0.02 N $AgNO_3$. 4.588 mg substance: 1.381 ml 0.02 N I_2. 4.503 mg substance: 1.321 ml 0.02 N I_2. Found %: Br 47.57, 47.62; S 9.64, 9.40. $C_7H_{10}O_3SBr_2$. Calculated %: Br 47.85; S 9.60.

Dioxides of 3-bromo-2,5-dimethyltetrahydro-1-thiopyran-4-one (III) and 5-bromo-2,5-dimethyltetrahydro-1-thiopyran-4-one (IV). a) 6.8 g of 2,5-dimethyltetrahydro-1-thiopyran-4-one dioxide (m.p.138°) was dissolved in 130 ml of glacial acetic acid, and 6.2 g of bromine was poured into the solution. The solution was vigorously stirred while being heated to 63-65°, at which temperature the solution was decolorized instantaneously. The solution was cooled and set aside to stand overnight. The next day 2.9 g of a crystalline dibromide with a m.p. of about 200° was filtered out of the reaction mass. Then the acetic acid was gradually driven off at a 30-mm vacuum, and another 7.9 g of bromide crystals was collected fractionally. The crystals collected constituted a mixture of the bromides (III) and (IV), which was separated into two fractions by fractional crystallization. The 5 g of crystals in the first fraction fused at about 200°. Two recrystallizations from acetone yielded the bromoketosulfone (III) with a m.p. of 195-200°.

23.410 mg subs.: 0.4588 ml 0.02 N $AgNO_3$. 25.900 mg subs.: 0.5042 ml 0.02 N $AgNO_3$. 3.455 mg subs.: 1.330 ml 0.02 N I_2. 3.970 mg subs.: 1.539 ml 0.02 N I_2. Found %: Br 31.26, 31.09; S 12.34, 12.42. $C_7H_{11}O_3SBr$. Calculated %: Br 31.32; S 12.56.

The second crystal fraction, totaling 4.3 g, fused at 130-135°. Six recrystallizations from acetic acid and alcohol yielded the bromoketosulfone (IV) with a m.p. of 144-145°.

22.876 mg subs.: 0.4392 ml 0.02 N $AgNO_3$. 26.064 mg subs.: 0.5038 ml 0.02 N $AgNO_3$. Found %: Br 30.78, 30.90. $C_7H_{11}O_3SBr$. Calculated %: Br 31.32.

The aggregate yield of the isomeric bromosulfones totaled 10.8 g, representing 88% of the theoretical yield.

b) 8.8 g of 2,5-dimethyltetrahydro-1-thiopyran-4-one dioxide (m.p. 138°) was dissolved in 100 ml of glacial acetic acid, and 1 ml of a 4N solution of hydrogen bromide in glacial acetic acid was added. The solution was vigorously stirred for 2 hours while 7.9 g of bromine in 20 ml of acetic acid was added. Then much of the acetic acid was driven off at a 25-30 mm vacuum. This yielded a mixture of the bromides (III) and (IV), from which 1.5 g of the high-melting bromide (III) with a m.p. of 199-200° was isolated. The residual mass fused at from 100° to 136°, 1.4 g of the low-melting monobromide (IV), with a m.p. of 144-145°, being isolated from it by fractional crystallization from alcohol. In addition, we secured 2.9 g of a fraction with a m.p. of 124-135° plus 2.5 g with a m.p. of 105-110°. When sodium acetate was used to split HBr from the last two fractions (see below), we secured 1.9 g of the sulfone (IX), corresponding to the low-melting monobromide (IV).

Dioxide of 3,5-dibromo-2-methylhexahydro-1-thiochroman-4-one (V). 5 g of 2-methylhexahydro-1-thiochroman-4-one dioxide (m.p. 157-158°) was dissolved in 40 ml of glacial acetic acid, 7.5 g of bromine was added to the solution, and the whole was vigorously stirred while it was heated to 85°. The solution was instantaneously decolorized at that temperature. As the solution cooled, 6.2 g of the dibromide settled out. Another 1.75 g of the dibromide settled out when part of the acetic acid was driven off in vacuo. The total yield was 7.9 g, or 91% of the theoretical. The dibromosulfone (V) consisted of colorless crystals with a m.p. of 186-187° (from alcohol).

8.144 mg subs.: 9.492 mg CO_2; 2.815 mg H_2O; 5.610 mg $SO_4 + Br$. Found %: C 31.81; H 3.87; S 8.75; Br 43.21. $C_{10}H_{14}O_3SBr_2$. Calculated %: C 32.10; H 3.77; S 8.57; Br 42.72.

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* The analysis was performed by the M.O.Korshun method, the percentages of Br and S being found from the total gain in weight [13].

In another test in which the bromine was added portionwise, 17% of the monobromide (VI) was secured in addition to the dibromide (V)

Dioxide of 3-bromo-2-methylhexahydro-1-thiochroman-4-one (VI). 4.3 grams of 2-methylhexahydro-1-thiochroman-4-one dioxide (m.p. 157-158°) was dissolved in 50 ml of glacial acetic acid, and 3.2 g of bromine was added to the solution. The solution was vigorously stirred as it was heated to 74°, at which temperature it was instantaneously decolorized. As the solution cooled, 2.4 g of the monobromide (VI), with an m.p. of approximately 215°, settled out. Another 1.5 g of crystals of the monobromide, with an m.p. of 202°, settled out when part of the acetic acid was driven off in vacuo. The monobromide totaled 3.4 g, representing 60% of the theoretical.

The bromosulfone (VI) consisted of colorless crystals with an m.p. of 215-216° (from alcohol).

4.194 mg substance: 6.210 mg CO_2; 1.895 mg H_2O. 3.370 mg substance: 5.010 mg CO_2; 1.520 mg H_2O; 2.005 mg SO_4 + Br. Found %: C 40.57, 40.56; H 5.06 5.05; S 10.82; Br 26.96. $C_{10}H_{15}O_3SBr$. Calculated %: C 40.57; H 5.12; S 10.86; Br 27.06.

II. Splitting Hydrogen Bromide Out of the Brominated Dioxides of Tetrahydro-γ-thiopyrones.

Dioxide of 2-methyl-1-thiopyran-4-one (VII). 8 grams of anhydrous sodium acetate[*] and 150 ml of acetone were placed in a three-necked round-bottomed flask fitted with a stirrer and a reflux condenser. The suspension was vigorously stirred as it was heated on a water bath to the boiling point of acetone, and a suspension of 6 g of the dibromosulfone (I) in 100 ml of acetone was poured into the flask during the course of an hour. Then boiling was continued for another half-hour. The liquid turned brown. After it had cooled the sodium bromide was filtered out, and the solution was acidulated with strong hydrochloric acid until it was clarified. Then the sodium chloride was filtered out, and the acetone was driven off, the residue crystallizing. This yielded 2.5 g of the sulfone (VII). Two recrystallizations from alcohol yielded 2.2 g of the pure substance with an m.p. of 141-141.5° (72% of the theoretical yield).

4.035 mg substance: 6.785 mg CO_2; 1.460 mg H_2O; 2.450 mg SO_4. Found %: C 45.90; H 4.05; S 20.27. $C_6H_6O_3S$. Calculated %: C 45.75; H 3.83; S 20.27.

Dioxide of 2,5-dimethyl-1-thiopyran-4-one (VIII). 8.8 grams of the dibromosulfone (II), 10.8 g of sodium acetate, and 50 ml of acetone were stirred and heated together for one hour on a water bath (60-65°). Then the solution was cooled and treated as described in the preceding experiment. This yielded 4.1 g of crude crystals. Two recrystallizations from alcohol yielded 3.4 g of pure crystals of the sulfone (VIII), with an m.p. of 139° (15% yield).

4.675 mg substance: 8.365 mg CO_2; 2.048 mg H_2O. 4.325 mg substance: 7.720 mg CO_2; 1.848 mg H_2O. 5.790 mg substance: 10.362 mg CO_2; 2.495 mg H_2O; 3.250 mg SO_4. Found %: C 48.83, 48.69, 48.84; H 4.90, 4.77, 4.82; S 18.74. $C_7H_8O_3S$. Calculated %: C 48.84; H 4.68; S 19.06.

Heating an alcoholic solution of the sulfone (VIII) with hydroxylamine hydrochloride yielded the oxime with an m.p. of 177.5-178° (from water).

3.827 mg substance: 0.259 ml N_2 (23°, 738 mm). 5.942 mg substance: 0.400 ml N_2 (21°, 734 mm). Found %: N 7.58, 7.48. $C_7H_9O_3NS$. Calculated %: N 7.48.

Dioxide of 2,5-dimethyl-2,3-dihydro-1-thiopyran-4-one (IX). 1.3 grams of the bromosulfone (IV) (m.p. 141-143°), 0.9 g of anhydrous sodium acetate and 25 ml of acetone were stirred together for one hour on a water bath at 60-65°. The test product was then processed like the preceding one. Recrystallization from alcohol yielded 0.6 g of the sulfone (IX) with an m.p. of 112.5-113° (66% yield).

5.221 mg substance: 9.258 mg CO_2; 2,800 mg H_2O; 2.880 mg SO_4. 4.773 mg substance: 8.468 mg CO_2; 2.491 mg H_2O; 2.625 mg SO_4. Found %: C 48.39, 48.42; H 6.00, 5.84; S 18.41, 18.40. $C_7H_{10}O_3S$. Calculated %: C 48.28; H 5.75; S 18.41.

The semicarbazone of the sulfone (IX) had an m.p. of 232-233° (from water).

Dioxide of 2,5-dimethyl-5,6-dihydro-1-thiopyran-4-one (X). 1.5 grams of the bromosulfone (III) (m.p. 199-200°), 25 ml of acetone, and 1 g of anhydrous sodium acetate were stirred together for one

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[*] The crystalline sodium acetate, $CH_3COONa \cdot 3H_2O$, may also be used.

hour on a water bath at 60-65°. After it had cooled the solution was filtered and treated as described above, yielding 1 g of crude crystals. Two recrystallizations from alcohol yielded 0.75 g of the sulfone (X) with an m.p. of 95° (73% yield).

5.199 mg substance: 9.224 mg CO_2; 2.842 mg H_2O; 2.860 mg SO_4. 5.042 mg substance: 9.000 mg CO_2; 2.708 mg H_2O; 2.775 mg SO_4. Found %: C 48.42, 48.71; H 6.11, 6.01; S 18.36, 18.37. $C_7H_{10}O_3S$. Calculated %: C 48.28; H 5.75; S 18.41.

The semicarbazone of the sulfone (X) had an m.p. of 206-207° (from water).

4.198 mg substance: 6.340 mg CO_2; 2.153 mg H_2O. Found %: C 41.21; H 5.74. $C_8H_{13}O_3N_3S$. Calculated %: C 41.56; H 5.68.

Dioxide of 2-methyl-5,6,7,8-tetrahydro-1-thiochromen-4-one (XI). 2.8 grams of the dibromosulfone (V) (m.p. 186-187°), 2.8 g of sodium acetate, and 50 ml of acetone were stirred together for one hour on a water bath at 60-65°. Processing yielded 1.3 g of the sulfone (XI) with an m.p. of 87-87.5° (from alcohol), constituting an 80% yield.

4.166 mg substance: 8.632 mg CO_2; 2.074 mg H_2O; 1.895 mg SO_4. 5.585 mg substance: 11.590 mg CO_2; 2.885 mg H_2O; 2.549 mg SO_4. Found %: C 56.55, 56.63; H 5.70, 5.78; S 15.28, 15.23. $C_{10}H_{12}O_3S$. Calculated %: C 56.58; H 5.70; S 15.11.

Dioxide of 2-methylhexahydro-1-thiochromen-4-one (XII). 2.3 grams of the bromosulfone (VI) (m.p. 215-216°), 2.8 g of sodium acetate, and 100 ml of acetone were heated for one hour as described above. The solution was faintly colored. Processing yielded 1.2 g of the colorless sulfone (XII) with an m.p. of 118-118.5° (from alcohol). The yield was 70%.

3.934 mg substance: 8.095 mg CO_2; 2.336 mg H_2O; 1.736 mg SO_4. 4.595 mg substance: 9.420 mg CO_2; 2.620 mg H_2O; 2.030 mg SO_4. Found %: C 56.15, 55.94; H 6.64, 6.38; S 14.73, 14.75 $C_{10}H_{14}O_3S$. Calculated %: C 56.05; H 6.58; S 14.96.

III. Condensation of Divinyl with Dioxides of the γ-Thiopyrones

Dioxide of 2-methyl-5,8,9,10-tetrahydro-1-thiochromen-4-one (XIII). 2 grams of the sulfone (VII) (m.p. 139-140°), 4 g of butadiene, 20 ml of dioxane, and 0.02 g of pyrogallol were heated together to 150° for 4.5 hours in a steel ampoule. After the ampoule had cooled, it was opened, and 1.2 g of the condensation product was filtered out of the reaction mixture. Driving the dioxane off in vacuo yielded another 1.2 g of crystals with an m.p. of 174-175°. The aggregate yield was 92%. The sulfone (XIII) consisted of lustrous needles with an m.p. of 177-177.5° (from alcohol or aqueous dioxane).

4.416 mg substance: 9.195 mg CO_2; 2.259 mg H_2O; 2.000 mg SO_4. Found %: C 56.82 H 5.72; S 15.12. $C_{10}H_{12}O_3S$. Calculated %: C 56.58; H 5.70; S 15.11.

An experiment run at 200° yielded the same sulfone (XIII), but more highly contaminated with butadiene polymers.

Dioxide of 2,10-dimethyl-5,8,9,10-tetrahydro-1-thiochromen-4-one (XIV). 1 gram of the sulfone (VIII) (m.p. 138-139°), 2 g of butadiene, 11 ml of dioxane, and 0.01 g of pyrogallol were heated to 210-215° for 5 hours in a steel ampoule. Driving off the solvent yielded 1.1 g of the crude product. Two recrystallizations from alcohol yielded 0.8 g of the sulfone (XIV) with an m.p. of 101-102° (61% yield).

5.050 mg substance: 10.858 mg CO_2; 2.870 mg H_2O. 6.486 mg substance: 13.935 mg CO_2; 3.755 mg H_2O; 2.798 mg SO_4. Found %: C 58.68, 58.63; H 6.34, 6.48; S 14.40. $C_{11}H_{14}O_3S$. Calculated %: C 58.40; H 6.24; S 14.18.

An experiment run at 160° yielded a mixture of the initial sulfone (VIII) and the condensation product (XIV).

Dioxide of 2,10-dimethyl-5,8,9,10-tetrahydro-1-thiochroman-4-one (XV). 1.5 grams of the sulfone (IX) (m.p. 112-113°), 2.4 g of butadiene, 16.5 ml of dioxane, and 0.02 g of pyrogallol were heated together to 195-200° in a steel ampoule for 6 hours. After the ampoule had cooled, it was opened and the solvent driven off, which yielded 1.5 g of crystals with an m.p. of 116-147°. Fractional crystallization from alcohol divided the mixture into two fractions with m.p. of 175-178° and 117-118°, respectively.

Repeated recrystallization of the first fraction from alcohol yielded needles of the sulfone (XVa) with an m.p. of 194.5-195.5°.

4.802 mg substance: 10.174 mg CO_2; 3.030 mg H_2O. 4.538 mg substance: 9.622 mg CO_2: 2.910 mg H_2O; 1.960 mg SO_4. Found %: C 57.82, 57.86; H 7.06, 7.17; S 14.42. $C_{11}H_{16}O_3S$. Calculated %: C 57.87; H 7.06; S 14.04.

Repeated recrystallization of the second fraction from alcohol yielded crystals of the isomeric sulfone (XVb) with an m.p. of 127-128°.

3.902 mg substance: 8.328 mg CO_2; 2.552 mg H_2O; 1.618 mg SO_4. 4.570 mg substance: 9.713 mg CO_2; 2.965 mg H_2O; 1.985 mg SO_4. Found %: C 58.24, 58.00; H 7.32, 7.26; S 13.84, 14.50. $C_{11}H_{16}O_3S$. Calculated %: C 57.84; H 7.06; S 14.04.

Heating the sulfone (X) with butadiene. 1.4 grams of the sulfone (X) (m.p. 95°), 2.5 g of butadiene, 15.4 ml of dioxane, and approximately 0.02 g of pyrogallol were heated together in a steel ampoule for 4 hours at 200°. Driving off the solvent yielded 1.1 g of crystals with an m.p. of 94-94.5° (from alcohol). Their mixed melting point with the original sulfone (X) exhibited no depression. The substance recovered was reheated with butadiene for 4.5 hours at 200° under the same conditions as before. Driving off the solvent yielded 0.950 g of crystals with an m.p. of 94-95°. Their mixed melting point with the original sulfone (X) exhibited no depression.

SUMMARY

1. Heating solutions of dioxides of tetrahydro-γ-thiopyrones in glacial acetic acid with bromine produces high yields of the corresponding mono- and dibromosulfones (I-VI).

Heating the bromosulfones (I-VI) with sodium acetate in acetone readily splits off hydrogen bromide, producing the corresponding dioxides of the thiopyrones and dihydro-1-thiopyrones (VII-XII), the yields ranging from 70 to 80%.

3. The sulfones (VII) and (VIII) enter into condensation with butadiene at 150-200° in a dioxane solution, forming the sulfone (XIII) with a 92% yield and the sulfone (XIV) with a 61% yield, respectively.

4. Condensing the sulfone (IX) with butadiene at 200° results in a 65% yield of two isomeric cis sulfones (XVa) and (XVb), differing in their configuration at the second carbon atom.

5. The sulfone (X) does not enter into a diene syntheses at temperatures up to 200°.

6. The ability of dioxides of substitution derivatives of the γ-thiopyrones to enter into a diene synthesis depends upon the position of the substitutent in the ring. Introducing a methyl group at the a position to the carbonyl group greatly hampers diene condensation, while introducing the methyl group at the β position to the carbonyl group renders this condensation impossible at temperatures up to 200°.

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N-ARYL SULFONYLQUINONIMINES [1]

S. I. Burmistrov and E. A. Titov

In our opinion the study of the reactions of the quinonimines and quinodiimines and their derivatives is of tremendous theoretical significance. For the quinonimines and quinondiimines always appear as intermediate products in the syntheses of many classes of dyes, namely: the quinonimine dyes (indophenols and indamines), the azines, the oxazines, the thiazines, and some of the azomethine dyes. We are justified in saying that the quinonimines and quinondiimines play the same great role, one might say extremely important role, in the syntheses of the foregoing groups of dyes that diazonium salts play in syntheses of azo dyes. The quinonimines and quinondiimines possess properties that approach those of the diazonium salts: extremely high reactivity and, as a result, instability. They differ from the diazonium salts, however, in being nonionic.

As we know, the N-acyl substitution derivatives of quinonimines (I) are equally nonionic compounds:

$$O =\!\!=\!\!\langle\ \rangle\!\!=\!\!= N-A \qquad (I)$$
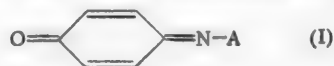
where A is an acid radical that can occur independently as the fairly stable anion A^-. Well-known members of this group of compounds are the quinonechlorimides and the quinonebromimides recently investigated by us [1,2]. These compounds do not contain an ionically bound halogen, but they can enter into reactions resembling the reactions of diazonium salts.

One of the most interesting reactions that link the quinonechlorimides to the diazonium salts, which is analogous to an azo coupling, is their reaction with phenols and amines, yielding indophenols and indamines. Determination of which N-substitution derivatives of the quinonimines can enter into the reaction in which indophenols are produced is of definite theoretical interest.

The formation of quinonebromimides and quinonebromodiimides and the reactions of the latter with phenols have led one of the present authors to describe a convenient specific reaction for p-aminophenols and p-diamines [2,3]. Observations of the quinonebromimide reaction of the N-aryl substitution derivatives of aminophenols indicated that the ordinary acyl substitution derivatives of p-aminophenol (II):
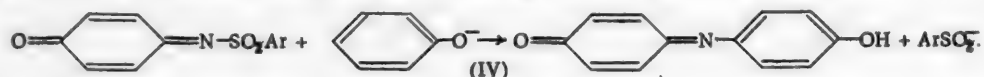
$$HO -\!\!\langle\ \rangle\!\!- NH-A \qquad (II)$$
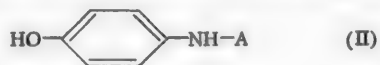
such as N-acetyl-1,4-aminophenol ($A = CH_3CO$) or N-benzoyl-1,4-aminophenol ($A = C_6H_5CO$) do not exhibit the quinonebromimide reaction. The N-aryl sulfonyl-1,4-aminophenols, which formed indophenols in the quinonebromimide reaction, in contrast to the compounds mentioned above, constituted an inexplicable exception at first sight. Since we could not suppose that the aryl sulfonyl radical would be split off and a quinonebromimide formed under the conditions of the quinonebromimide reaction, we assumed that N-aryl sulfonylquinonimines, which were able to react with the phenols and form indophenols, were produced in a simple oxidation reaction. We therefore chose as the objective of the present research the synthesis of the hitherto unknown N-aryl sulfonylquinonimines and a study of their properties. Our investigations resulted in the synthesis of some representatives of a new class of compounds (III).

$$O =\!\!= Ar'' =\!\!= N-SO_2Ar \qquad (III)$$

[1] Compounds containing the =NH group are named differently in the literature: as imines and as imides. In the Beilstein handbook the single terminology: imides, has been adopted; it did not persist, however. We have retained the latter term solely for N-halogenated imines.

where $Ar^{\bullet}$ is an aromatic group, an arylene, a constituent of the quinonimine residue, and Ar is an aromatic radical, an aryl. The synthesis was effected by oxidizing the N-aryl sulfonyl-1,4-aminophenols (II) with bichromate in the cold in dilute sulfuric acid.

The synthesized compounds proved to be yellow or yellow-orange crystalline substances, in contrast to the quinonechlorimides and quinonebromimides, they resisted heat fairly well and therefore exhibited sharp melting points. Noteworthy among the other properties of the substances we synthesized was their indophenol reaction, that is, the appearance of a blue (or violet) coloration when reacted with phenol or 1-naphthol in an alkaline medium. We made a thorough study of this reaction, finding that N-aryl sulfonylquinonimines react with phenol in an alkaline medium by splitting off the aryl sulfonyl residue as an anion of an aryl sulfinic acid. The stoichiometric equation for this transformation may be written as follows:

$$O=\!\!\left\langle\right\rangle\!\!=\!N-SO_2Ar + \left\langle\right\rangle\!-O^- \rightarrow O=\!\!\left\langle\right\rangle\!\!=\!N\!-\!\left\langle\right\rangle\!-OH + ArSO_2^-$$

$$(IV)$$

The N-aryl sulfonylquinonimines we investigated can be readily reconverted into aryl sulfonylaminophenols by the action of reducing agents. Derivatives of 1,4-benzoquinone react quantitatively with potassium iodide in an acid medium liberating iodine. This latter reaction was utilized to identify the compounds by determining their oxidation equivalents.

An aryl sulfonylquinonimine and an N-aryl sulfonyl-1,4-aminophenol constitute a reversible oxidation-reduction system, like the quinone-hydroquinone system. In contrast to the quinones, aryl sulfonylquinonimines are not colored by acetoacetic ester in ammonia. When aryl sulfonylquinonimines are heated with 20% sulfuric acid, they decompose, yielding quinone. The properties of the synthesized compounds are given in the following table.

Properties of N-Aryl Sulfonylquinonimines

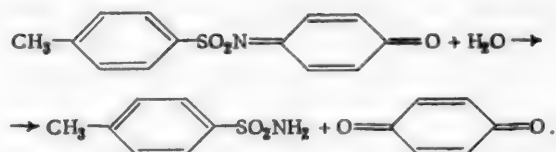| No.	Name	Formula	Melting point	Indophenol reaction	
				With phenol	With 1-naphthol
1	N-p-Toluenesulfonyl-1,4-benzoquinon-imine	$CH_3C_6H_4SO_2N=\!\!\left\langle\right\rangle\!\!=O$	126.5°	Blue	Violet
2	N-Benzenesulfonyl-1,4-benzoquinon-imine	$C_6H_5SO_2N=\!\!\left\langle\right\rangle\!\!=O$	137	"	"
3	N-p-Toluenesulfonyl-1,4-naphthoquinon-imine	$CH_3C_6H_4SO_2N=\!\!\left\langle\right\rangle\!\!=O$	156	—	Blue

As may be readily seen, aryl sulfonylquinonimines exhibit the same indophenol reaction as the quinonebromimides [2].

EXPERIMENTAL

The N-aryl sulfonyl-1,4-aminophenols required for synthesizing the aryl sulfonylquinonimines were prepared by acylating 1,4-aminophenols with the respective aryl sulfochlorides in a water-soda suspension.
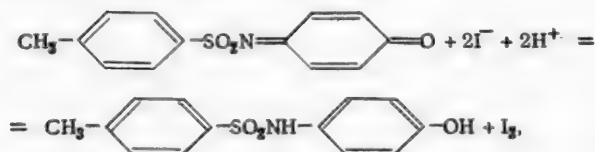
N-p-Toluenesulfonyl-1,4-aminophenol. 84.8 grams of soda (0.8 mole — 100% excess) was dissolved in 400 ml of water, 64.2 g (0.40 mole) of 1,4-aminophenyl hydrochloride was added to the soda solution, and then 76.2 g (0.4 mole) of p-toluene sulfochloride was added at room temperature. The mixture was refluxed on a water bath and constantly stirred with a mechanical stirrer until the odor of toluene sulfochloride had disappeared, which took 2.5 hours. When the reaction was over, the mixture was cooled, and the precipitated toluenesulfonyl derivatives were filtered out, washed with water, and dried. The yield was nearly quantitative (103 g). The substance was purified by recrystallizing it from a large quantity of water; the m.p. of the recrystallized product was 144.5°, the literature giving the m.p. of N-p-toluenesulfonyl-1,4-hydroxyanilide as 143° [4].

<u>N-p-Toluenesulfonyl-1,4-benzoquinonimine.</u> 10 grams of finely pulverized N-p-toluenesulfonyl-1,4-aminophenol was added at room temperature to a solution of 5.7 g of sodium dichromate ($Na_2Cr_2O_7 \cdot 2H_2O$) in 175 ml of 20% sulfuric acid. The mixture was stirred for 50 minutes and then diluted with water, the precipitate being filtered out. The precipitate was washed on the filter with water and finally washed with alcohol to eliminate part of the unreacted toluenesulfonyl-1,4-aminophenol. The yield ranged from 7.9 to 8.4 g, or 79%-84% of the theoretical. Refining is best accomplished by crystallization in small portions from alcohol, taking care to avoid prolonged heating in the alcohol solution, as we found that aryl sulfonylquinonimines are reduced when heated for a long time in alcohol, while the alcohol is oxidized, as is noticeable by the odor of acetaldehyde. The refined crystalline product had an m.p. of 126.5°. Analysis indicated that it contained sulfur and nitrogen. Orange-yellow crystals that turned into a yellow powder when pulverized; freely soluble in ether, benzene, and glacial acetic acid, slightly soluble in cold alcohol, more soluble in hot alcohol, and very slightly soluble in water. In ammonia, it colored phenol blue and 1-naphthol violet. The reaction involved in the production of indophenols was rapid at room temperature. Heating with 20% sulfuric acid on a water bath yielded 1,4-benzoquinone, which was distilled with steam. The distillate was an aqueous solution with the odor of quinone; it is turned blue by acetoacetic ester and ammonia: the quinone reaction [5]. It is likely that in the first stage of acid hydrolysis 1,4-benzoquinone and p-toluene-sulfamide are produced:

$$CH_3 - \langle\ \rangle - SO_2N = \langle\ \rangle = O + H_2O \longrightarrow$$

$$\longrightarrow CH_3 - \langle\ \rangle - SO_2NH_2 + O = \langle\ \rangle = O .$$

Since the initial toluenesulfonyl-1,4-aminophenol was very readily soluble in alcohol, washing with alcohol was a convenient method of separating the unoxidized compound from the oxidized one. Oxidation with chromic anhydride in glacial acetic acid produced an 80% yield of toluenesulfonylquinonimine. Attempts to secure this product by oxidizing with a suspension of lead dioxide in benzene met with failure, the yields being extremely low.

The product was analyzed by determining its oxidation equivalent. This was done by dissolving a sample of the toluenesulfonylquinonimine in alcohol, and adding 20% sulfuric acid and an excess of potassium iodide. The iodine liberated in the stoichiometric equation:

$$CH_3 - \langle\ \rangle - SO_2N = \langle\ \rangle = O + 2I^- + 2H^+ =$$

$$= CH_3 - \langle\ \rangle - SO_2NH - \langle\ \rangle - OH + I_2,$$

was back-titrated with thiosulfate. After the thiosulfate titration colorless thin needles settled out; they were filtered out and dried, and exhibited the melting point of the original toluenesulfonyl-1,4-aminophenol.

0.1993 g substance: 15.13 ml 0.1 N $Na_2S_2O_3$. 0.2002 g substance: 15.14 ml 0.1 N $Na_2S_2O_3$. Found: equiv. 131.7, 132.1. $\frac{1}{2}C_{13}H_{11}O_3NS$. Calculated: equiv. 130.65. 0.1993 g substance: 7.70 ml 0.1 N HCl (Kjeldahl) Found %: N 5.41. $C_{13}H_{11}O_3NS$. Calculated %: N 5.36.

<u>N-Benzenesulfonyl-1,4-aminophenol.</u> This was similarly prepared from 1,4-aminophenol hydrochloride and benzene sulfochloride. Crystallization from water yielded barely pinkish flat needles, m.p. 155°. The literature gives m.p. 153° [6] and 156.5° [7]. They are very freely soluble in cold alcohol.

<u>N-Benzenesulfonyl-1,4-benzoquinonimine.</u> 10 grams of benzenesulfonyl-1,4-aminophenol was ground to a powder and added to a solution of 6 g (50% excess) of sodium dichromate ($Na_2Cr_2O_7 \cdot 2H_2O$) in 180 ml of 20% sulfuric acid. The mixture was stirred vigorously for 1 hour 15 minutes, then diluted with water to make 400 ml, and the precipitate filtered out. The dry precipitate weighed 7 g (70% of the theoretical) after it had been washed with water until its reaction was neutral to eliminate the acid and with alcohol to eliminate the unoxidized product. Further purification followed the lines of the preceding synthesis, employing careful crystallization from alcohol. This yielded orange-yellow crystals, or a yellow powder, m.p. 137°, which

contained sulfur and nitrogen. It was freely soluble in ether, benzene, and glacial acetic acid, and slightly soluble in cold alcohol. It colors phenol blue and 1-naphthol violet. It stains the skin brown, like quinone-chlorimide and quinonebromimide. The synthesized compound was analyzed by determining its oxidation equivalent by titrating the iodine liberated from potassium iodide in an acid medium with thiosulfate and then determining the nitrogen by the Kjeldahl method:

0.0684 g substance: 5.32 ml 0.1 N Na$_2$S$_2$O$_3$. 0.0644 g substance: 5.02 ml 0.1 N Na$_2$S$_2$O$_3$. Found: equiv. 128.4, 128.5. $\frac{1}{2}$C$_{12}$H$_9$O$_3$NS. Calculated: equiv. 123.65. 0.2143 g substance: 8.77 ml 0.1 N HCl (Kjeldahl). Found %: N 5.73. C$_{12}$H$_9$O$_3$NS. Calculated %: N 5.67.

N-p-Toluenesulfonyl-1,4-aminonaphthol. 19.9 grams of 1,4-aminonaphthol hydrochloride, produced by the method [8] was added to a solution of 21.2 g of soda (0.2 mole) in 400 ml of water. After some time had passed, 19.1 g of p-toluene sulfochloride was added at room temperature. The whole was vigorously stirred as its temperature was raised to 70°, being kept at that temperature until the odor of toluene sul-fochloride had disappeared (about 2.5 hours). Then the precipitate was filtered out, washed with water, and dried. It was refined by recrystallization from xylene. This yielded pinkish-gray crystals that were readily soluble in alcohol, slightly soluble in cold benzene and xylene, more so in hot xylene, and in-soluble in water. M.p. 183°. Qualitative analysis indicated that sulfur and nitrogen were present. The sub-stance exhibited the quinonebromimide reation with 1-naphthol only (blue coloration), while a paper test showed that it combined with 4-nitrophenyldiazonium.

0.2705 g substance: 8.55 ml 0.1 N HCl (Kjeldahl). Found %: N 4.43. C$_{17}$H$_{15}$O$_3$NS. Calculated %: N 4.47.

N-p-Toluenesulfonyl-1,4-naphthoquinonimine. 10 grams of N-p-toluenesulfonyl-1,4-aminonaphthol was placed in a solution of 4.75 g of sodium dichromate (Na$_2$Cr$_2$O$_7$·2H$_2$O) in 145 ml of 20% sulfuric acid. After the mixture had been stirred for 3 hours at room temperature, the precipitated oxidized product was filtered out and washed with water and then with alcohol. Crystallization from alcohol yielded red-yellow lamellae, m.p. 156°. Freely soluble in benzene, very slightly soluble in cold alcohol, and insoluble in water. In contrast to the previous two compounds, it does not liberate iodine quantitatively from potassium iodide and does not color phenol in ammonia, though it does color 1-naphthol blue, like 1,4-naphthoquinonebromimide.

0.2001 g substance: 6.53 ml 0.1 N HCl (Kjeldahl). Found %: N 4.57. C$_{17}$H$_{13}$O$_3$NS. Calculated %: N 4.50.

Study of the indophenol reaction of N-toluenesulfonyl-1,4-benzoquinonimine. We investigated the reaction products of toluenesulfonyl-1,4-benzoquinonimine and phenol in ammonia in order to explore the stoichiometric equation governing the production of indophenols from the aryl sulfonylquinonimines. 4.36 g of N-p-toluenesulfonylquinonimine was agitated with an ammoniacal solution of 2.4 g of phenol. This pro-duced a strong blue coloration. After the intensity of the coloration had reached a constant value, the ammoniacal solution was filtered to remove the unreacted N-p-toluenesulfonylquinonimine. The solution was then carefully neutralized with acetic acid to eliminate the indophenol produced. The red-brown pre-cipitate was filtered out, the dissolved indophenol being extracted with benzene. The red-brown precipi-tate had an m.p. of 59°; the m.p. being raised to 160° after crystallization from acetone. The substance exhibited all the properties of the indophenol (IV).

The literature gives the m.p. of the indophenol with this structure as 160° [9]. It dissolves in ammonia and alkali, coloring them blue.

After the indophenol had been extracted with benzene, the aqueous layer was acidulated and then extracted with ether. Evaporation of the ether yielded pinkish crystals with an m.p. of 85°. The m.p. of p-toluenesulfinic acid is 86° according to the literature [10]. p-Thiocresol was produced by reduction with zinc and sulfuric acid in order to prove that the synthesized product was the same as p-toluenesulfinic acid. We secured a solution that had the intense odor of thiocresol. The thiocresol was driven off with steam. The recovery of indophenol and p-toluenesulfinic acid from the reaction medium confirmed the stoichio-metric equation given in the preceding theoretical section for the formation of indophenols from aryl sulfonyl-quinonimines. Hence, the aryl sulfonyl residue is split off as an anion of an aryl sulfinic acid, as demon-strated above. This is all the more remarkable inasmuch as it is ordinarily very difficult to split an aryl sulfonyl residue from its bond to a nitrogen atom. In this instance the cleavage is effected by extremely weak agents in the cold.

SUMMARY

1. Three N-aryl sulfonylquinonimines have been synthesized for the first time, and their properties and reactions are described.

2. N-Aryl sulfonylquinonimines that are derivatives of 1,4-benzoquinone liberate iodine quantitatively from iodides in an acid solution.

3. The N-aryl sulfonylquinonimines react with phenol and 1-naphthol, yielding indophenols, the aryl sulfonyl residue splitting off as an anion of an aryl sulfinic acid.

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QUINONIODIMIDES AND QUINONEDIIODODIIMIDES [1]

S. I. Burmistrov and V. I. Glaskov

In connection with the general plan of our research on the properties and reactions of N-substitution derivatives of the quinonimines, we described quinonebromimides and quinonedibromodiimides [1,2] and N-aryl sulfonylquinonimines [3] in our previous papers. The present research deals with the synthesis and an investigation of the properties and reactions of the hitherto undescribed quinone-N-iodimides and quinone-N,N'-diiododiimides. As might have been expected, it was much harder to synthesize the latter compounds because of the lower stability of the substances investigated. To this there were added the difficulties arising from the low stability of alkaline solutions of the hypoiodites. We have synthesized three quinonediiododiimides and secured them in the individual state; in an attempt to synthesize 1,4-benzoquinone-iodimide we secured a yellow crystalline substance that decomposed rapidly, turning dark and giving off iodine. This made it impossible to isolate it or analyze it. We proved that the unstable compound was 1,4-benzoquinoniodimide by demonstrating the existence of the indophenol reaction (formation of blue indophenols with alkaline solutions of phenol) and then by analyzing the benzene solutions for their iodine content by the iodate method and by determining their oxidative titer.

The synthesized quinonediiododiimides proved to be more intensely and deeply colored than the analogous quinonedichlorodiimides and quinonedibromodiimides; like the latter, they react with phenols in an alkaline solution, producing intensively colored indophenols. Like the quinonedibromodiimides, the quinonediiododiimides, as derivatives of quinones with a high oxidation potential, liberate iodine quantitatively from acid solutions of iodides in accordance with the following stoichiometric equation:

$$IN = \underset{}{\bigcirc}^{R} = NI + 4H^+ + 4I^- = H_2N - \underset{}{\bigcirc}^{R} - NH_2 + 3I_2.$$
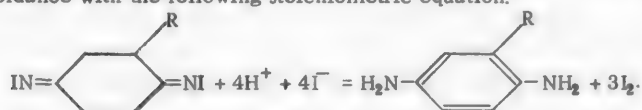
This reaction was employed to analyze and identify the quinonediiododiimides. The quinonediiodidiimides are much less soluble in nonpolar solvents than the analogous quinonedibromodiimides and are light-sensitive. As might be expected the low stability of the quinonediiodidiimides is due to the slight energy of the N—I bond; that is why comparatively little energy is required to cleave them, yielding free atoms of iodine.

The following table gives the properties of the synthesized quinoniodimide and quinonediiododiimides.
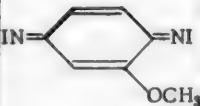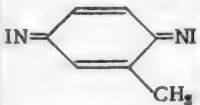
EXPERIMENTAL

Owing to the instability of the compounds mentioned, rapid operations at solution temperatures of the order of 0° are essential conditions for their successful isolation. The following procedure was employed to prevent decomposition of the hypoiodite: finely pulverized iodine was added to a chilled alkali solution, and then the solution of aminophenol or of the p-diamine, was rapidly added, with stirring, without waiting for the iodine to dissolve, the resultant precipitate being quickly filtered out on a suction filter and washed with water and then with ether.

1,4-Benzoquinoniodimide. Because the free compound is so unstable, only benzene solutions of it were secured, the solutions being analyzed as set forth below.

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[1] Compounds containing the =NH group are named differently in the literature: as imines and as imides. In the Beilstein handbook the latter term is used throughout but it did not persist in the chemical literature, however. We have retained the latter term solely for N—halogenated imines (quinonechlorimides, quinonebromimides, etc.)

Properties of Quinoniodimide and Quinonediiododiimides

No.	Name	Formula	Decomposition temp.	Appearance
1	Benzoquinoniodimide	O=⟨ ⟩=NI		Reddish-yellow crystals
2	1,4-Benzoquinonediiododiimide	IN=⟨ ⟩=NI	60°	Golden-yellow crystals
3	2-Methoxy-1,4-benzoquinonediiododiimide	IN=⟨ ⟩=NI, OCH₃	65	Yellow crystals
4	2,5-Toluquinonediiododiimide	IN=⟨ ⟩=NI, CH₃	77	Reddish-yellow crystals

A solution of 6.5 g of NaOH (0.16 mole) in 115 ml of water was chilled to −5° and stirred mechanically while 10.2 g (0.04 mole) of finely powdered iodine was added. A previously prepared solution of 1.09 g (0.01 mole) of 4-aminophenol in 100 ml of water + 2 g of NaOH was then immediately added to the alkaline suspension of iodine, a reddish-yellow precipitate settling out. Benzene was added to extract the quinoniodimide, and the mixture was agitated. After the crystals had dissolved in the benzene, the benzene solution was separated, washed with water, and dried with calcium chloride. The yellow benzene solution was fairly stable: for analysis it was diluted with more benzene in order to obtain a 1/40-molar solution, based on 1,4-benzoquinoniodimide.

The presence of 1,4-benzoquinoniodimide in the benzene solution was proved by the following qualitative reactions: a drop of the benzene solution applied to paper turned an intense blue when treated with phenol in ammonia; the colored benzene solutions were decolorized by reducing agents. We determined the oxidative titer and the percentage of iodine by the iodate method in order to prove that the solution contained 1,4-benzoquinoniodimide.

Determination of the oxidative titer. An Aqueous solution of KI and 10% sulfuric acid were added to the benzene solution. The liberated iodine was back-titrated with thiosulfate. Titration of the iodine liberated from 20 ml of the benzene solution consumed: I) 11.2 ml; II) 11.2 ml of 0.1 N $Na_2S_2O_3$. Oxidative titer:

$$\frac{11.2 \cdot 0.1}{20} = 0.056 \text{ mg-equivalent per ml.}$$

Determination of the iodine [4]. 15 ml of a 20% alcoholic solution of KOH was added to 20 ml of the benzene solution, the mixture was boiled for 10 minutes, and the alcohol and benzene were evaporated in a porcelain dish. The residue was calcined and dissolved in water, the solution being diluted to 100 ml in a 100-ml measuring flask. 50 ml of the resultant aqueous solution was neutralized with acid, an excess of chlorine water being added to convert the iodide into an iodate. The solution was heated and then boiled to eliminate the excess chlorine. After the excess chlorine had been driven off, KI and 10% sulfuric acid were added. The liberated iodine was back-titrated with thiosulfate. 10 ml of the original benzene solution (allowing for the dilution) required the following amounts of thiosulfate: Test I: 8.3 ml of 0.1 N $Na_2S_2O_3$; Test II: 8.5 ml of 0.1 N $Na_2S_2O_3$. Whence the amount of iodine (as a compound) was: Test I: $\frac{8.3 \cdot 0.1}{6 \cdot 10} = 0.0138$ mg-atom per ml; Test II: $\frac{8.5 \cdot 0.1}{6 \cdot 10} = 0.0141$ mg-atom per ml.

The analysis shows that each gram-atom of iodine in the compound corresponds to 4 oxidation equivalents. The only possible explanation of this is that the solution contains quinoniodimide, which reacts with the iodide in an acid solution as follows:

$$O=⟨\ ⟩=NI + 3H^+ + 3I^- = HO-⟨\ ⟩-NH_2 + 2I_2.$$
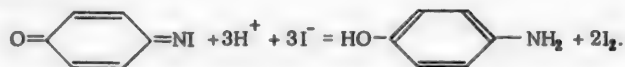
We have thus proved that the benzene solution contains 1,4-benzoquinoniodimide.

1,4-Benzoquinonediiododiimide. A solution of 13 g (0.32 mole) of NaOH in 50 ml of water was chilled to 0° and 20.3 g of finely powdered iodine (0.08 mole) was added. A solution of 1.08 g (0.01 mole) of 1,4-phenylenediamine in 100 ml of water was added at once to the suspension. The golden-yellow precipitate was filtered out quickly, washed with water, then with ether. Attempts to crystallize the substance were fruitless: it broke down, yielding iodine. The dried precipitate was used for analysis. This was done by dissolving a sample of the substance in benzene and adding an aqueous solution of potassium iodide and 10% sulfuric acid, the iodine liberated being

back-titrated with thiosulfate. The equation for this reaction is given in the theoretical section of this paper.

0.0368 g subs.: 6.8 ml 0.1 N $Na_2S_2O_3$. 0.1386 g subs.: 24:2 ml 0.1 N $Na_2S_2O_3$.
Found: equiv. 58.9, 60.9. $\frac{1}{6}C_6H_4N_2I_2$. Calculated: equivalent 59.66.

2-Methoxy-1,4-benzoquinonediiododiimide. The 2,5-diaminoanisole required for this synthesis was prepared by reducing 5-nitro-2-aminoanisole with zinc dust in an aqueous-alcoholic solution containing NaCl, as described in a previous paper [2]. The excess zinc dust and the zinc oxide were filtered out of the solution, which was then diluted with water so as to produce an approximately half-molar solution of 2,5-diaminoanisole. 20 ml of this solution was added, as before, to a suspension of 20.3 g of finely powdered iodine in a solution of 13 g of NaOH in 200 ml of water. It was found advisable to employ more highly diluted solutions than indicated for the synthesis of 1,4-benzoquinonediiododiimide. The yellow precipitate was quickly filtered out and washed with water. The precipitate was purified by dissolving it in dichloroethane at 35°, filtering out the undissolved impurities, shaking with calcium chloride to remove the water, and chilling to −15°. The precipitated yellow crystals were filtered out rapidly and dried. The substance breaks down when heated to 65°; it colors phenol in ammonia blue; and it colors 1-naphthol blue, thus differing from the preceding compounds. It was analyzed by determining its oxidation equivalent.

0.0516 g subs.: 8.5 ml 0.1 N $Na_2S_2O_3$. 0.0941 g subs.: 15.4 ml 0.1 N $Na_2S_2O_3$.
Found: equiv. 66.6, 66.3. $\frac{1}{6}C_7H_6ON_2I_2$. Calculated: equiv. 64.66.

2,5-Toluquinonediiododiimide. The 2,5-diaminotoluene required for the synthesis was prepared by reducing 5-nitro-2-aminotoluene as indicated above [2]. The aqueous solution was employed as it was in synthesizing the diiododiimide, the remainder of the synthesis procedure resembling that outlined above. Crystallization from dichloroethane   yielded the substance as reddish-yellow crystals. It decomposes when heated to 77°. It colors phenol in ammonia blue. It was analyzed by determining its oxidation equivalent.

0 0274 g subs.: 4.8 ml 0.1 N $Na_2S_2O_3$. 0 0788 g subs.: 13 4 ml 0.1 N $Na_2S_2O_3$.
Found. equiv 62.1, 64 0. $\frac{1}{6}C_7H_6N_2I_2$.   Calculated: equiv. 62.0.

SUMMARY

1. Three quinonediiododiimides, constituting a new class of compounds, have been synthesized for the first time.

2. It has been proved that when p-aminophenol is reacted with hypoiodite, 1,4-benzoquinoniodimide is produced.

3. The physical properties and the reactions of the new compounds have been described.

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RESEARCH ON IMIDAZOLE DERIVATIVES

III. NITRATION OF DERIVATIVES OF BENZIMIDAZOLE

## AND SYNTHESIS OF SOME NEW DERIVATIVES OF 1,2,4,5-DIIMIDAZOLOBENZENE [1]

L. S. Efros

When doing research on the behavior of benzimidazole and its derivatives in substitution reactions, the first thing we must bear in mind is the tautomerism of these compounds, manifested in the fact that the hydrogen in the imino group of the heterocyclic ring can shift from one nitrogen atom to another. Such a tautomeric shift of the hydrogen atom causes no change in the molecule of the unsubstituted benzimidazole, but ought to yield two different compounds when it occurs in asymmetrical derivatives of the latter:
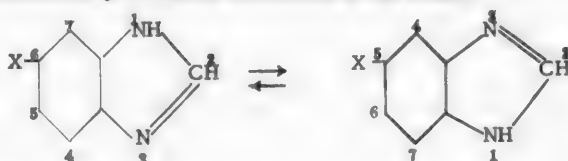

This is why these substances are given a dual name in F.F.Beilstein's well-known handbook and in many scientific papers, as an indication that they can occur in both tautomeric forms. No instance of desmotropism of benzimidazole derivatives has been described in the literature up to now, however, which is an obvious indication of the great ease with which one substance is converted into the other. The reason for this, in our opinion, is the amphoteric nature of the compounds in question, so that the tautomeric shift can occur in an acid or an alkaline medium.

In the present report we have attempted to settle the question of the effect exerted by the tautomerism of the imidazole group upon the benzene ring when benzimidazole derivatives are nitrated. In this reaction, which takes place in an acid medium, the benzimidazole derivatives must act as cations, in which the equivalent nitrogen atoms of the heterocyclic ring can transfer their electrons to para and ortho positions of the benzene ring, thus facilitating the entrance of electrophilic substituents. Actually, benzimidadole and its 2-substitution derivatives are nitrated extremely easily, as several researchers had discovered long before our investigations [2], the nitro group entering at the 5 and 6 positions of the benzimidazole group exclusively, these being para positions with respect to the nitrogen atoms of the heterocyclic ring. Whenever one of these positions is occupied by a Class I substituent, such as methyl, methoxy, or acetylamino group, the nitro group selectively enters the other free para position to the 5 or 6 nitrogen atom of the heterocyclic ring [3]. In the light of these findings the results of the research by Kym and Ratner [4], who made a study of a second nitration of 2-hydroxy-5-nitrobenzimidazole (I) and of 2-methyl-5-nitrobenzimidazole (II), seem to be quite unexpected.
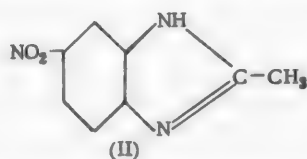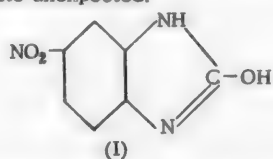

These researchers discovered that the compound (I) enters into this reaction with great ease, while the compound (II) requires rather severe conditions, the nitro group entering these compounds at the 5 (or 6) position as before, producing the ortho dinitro products (III) and (IV).
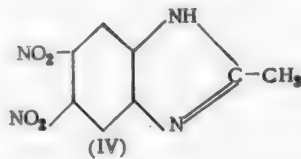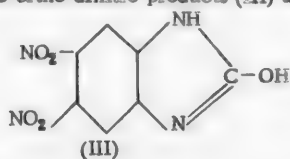
Wishing to check these findings, we readily synthesized 5,6-dinitro-2-methylbenzimidazole (IV) and reduced it to the corresponding diamine (V). We then employed the method of condensing ortho diamines with carboxylic acids under pressure in the presence of hydrochloric acid described by us previously, which results in the formation of imidazole rings [5], to secure high yields of the previously described [4] methyl- and dimethyldiimidazolo-1,2,4,5-benzene (VI) and (VII).
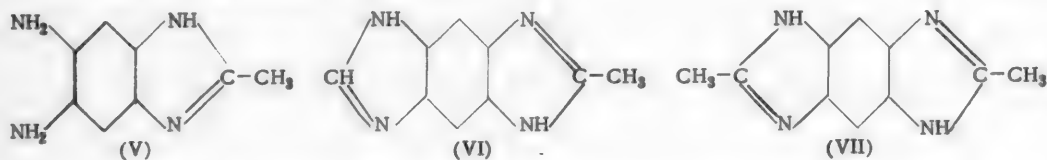

The similarly constructed derivatives of diimidazolo-1,2,4,5-benzene: (VIII), (IX), (X), and (XI), not described in the literature before, were synthesized under the same conditions, by condensing the diamine (V) with benzoic, phenylacetic, phenylpropionic, and 2-phenylbenzimidazole-5-carboxylic acids, respectively, the yields being uniformly satisfactory.
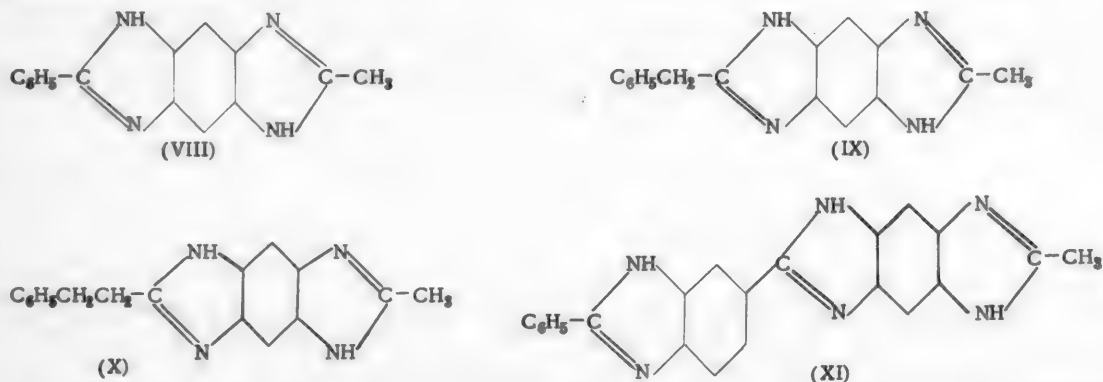

It might have been thought that the unexpected course taken by the nitration reaction in the case of the compounds (I) and (II) was somehow related to the influence of the substituents located at the 2 position [6]. We therefore thought it important to study the nitration of unsubstituted benzimidazole, which we proceeded to do.

By nitrating benzimidazole under conditions that differed somewhat from those described in the literature [7] we readily obtained the mononitro derivative (XII), to which another nitro group could be added when the conditions were severe enough; separating the dinitro product (XIII) from the unreacted mononitro derivatives involved considerable difficulty, however. Reducing the compound (XIII) by tin and hydrochloric acid, we obtained the corresponding diamine (XIV), which we could not secure in the chemically pure state owing to its extraordinarily low resistance to oxidation.
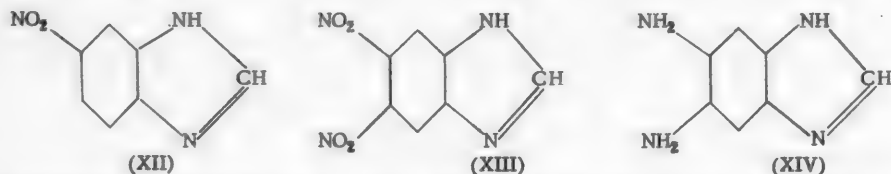
But, by condensing this compound with acetic acid under the conditions described above, we secured a good yield of a derivative of diimidazolo-1,2,4,5-benzene (VI), identified with the compound synthesized previously by condensing the diamine (V) with formic acid. This confirmed the structure of the dinitro product (XIII). Condensing the diamine (XIV) with benzoic, phenylacetic, phenylpropionic, and 2-phenylbenzimidazole-5-carboxylic acid yielded the derivatives of diimidazolo-1,2,4,5-benzene (XV), (XVI), (XVII), and (XVIII), respectively, which have not been described previously, and were purified as their hydrochlorides:

(XV) C–C₆H₅ → $C–C_6H_5$

(XV) $C–C_6H_5$

(XVI) $C–CH_2C_6H_5$

**(XVII)** $C–CH_2CH_2C_6H_5$

(XVIII) $C–C_6H_5$
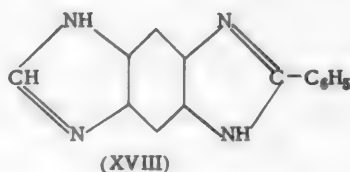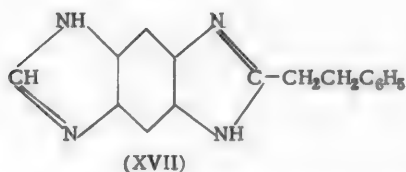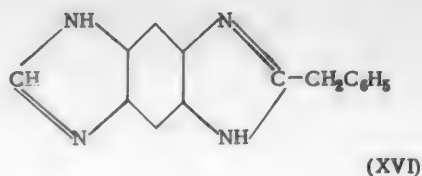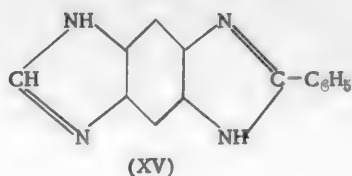
Hence, the singular course of the nitration of benzimidazole derivatives cannot be attributed to the influence of the substituent at the 2 position. It is likewise obvious that the substituent present in the benzene ring of benzimidazole has no decisive effect upon the course of this reaction in the cases considered. Benzimidazole evidently cannot be regarded merely as a derivative of benzene that contains two substituents in an ortho position to each other. This compound, like, say, naphthalene, possesses its own singularities, which are manifested in the nitration reaction, governing its direction, and consist of the following: 1) the 5 and 6 positions are more reactive than the 4 and 7 positions; and 2) the 5 and 6 positions behave only very slightly as ortho positions, in this respect resembling the 2 and 3 positions of naphthalene.

It seems to us that the sole explanation for the origin of these specific peculiarities is the fact that the imidazole group deforms the benzene ring of the benzimidazole considerably, destroying its symmetry. This gives rise to a double linkage between the carbon atoms common to the benzene and imidazole rings as well as between the 4-5 and 6-7 positions, while the bond between the 5 and 6 carbon atoms tends to become a single bond (XIX).

With this arrangement of the bonds, benzimidazole ought to have chemical properties that resemble those of naphthalene. In contrast to the latter, however, our compound exhibits higher reactivity at the 5 and 6 positions instead of the 4 and 7 positions, though the former positions correspond to the less active β-positions in naphthalene. The reason for this singularity in benzimidazole is the orienting effect of the nitrogen atoms in the heterocyclic ring, which is transmitted via the chain of conjugated bonds. The 5 and 6 positions prove to be the reactive ends of the chain because, we believe, there is some break in conjugation between these positions (XX).

If there is any substituent present at one of these positions, say, 5, it can exert influence only toward the 4 position, its influence upon the 6 position, which is linked to the 5 position by a single bond, being very slight. If the substituent is a Class II one, such as a nitro group, the succeeding substituent can enter at the 6 position, as we have demonstrated previously. But if the substituent attached to the 5 position is a Class I one, we ought to find

(XIX)

(XX)

discordant orientation present: whereas this substituent promotes the reaction at the 4 position most, the imino group in the heterocyclic ring promotes a reaction at the 6 position. In this case the substituting group can evidently enter at both of these positions, though this depends upon the strength of the effect exerted by the Class I substituent already present. This is fully borne out by the findings in the literature. When 5-chloro- or 5-methyl- or 5-ethoxybenzimidazole is nitrated with potassium nitrate, for example, we can readily obtain [8] 4,6-dinitro derivatives, the first nitro group being added at the 6 position.
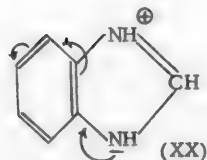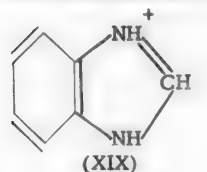
The experiments of K. Fries and his co-workers [9] on the chlorination and bromination of derivatives of 5-hydroxybenzimidazole demonstrated that the first halogen atom enters at the 4 position, position 6 being substituted only later. Thus, the effect of the hydroxy group is greater in this case than the specific activity of the 6 position of the benzimidazole group. Fries also discovered the great readiness with which benzimidazole derivatives produce 4,5-quinones, and the impossibility of producing a quinone at the 5 and 6 positions, which is further confirmation of our hypothesis concerning the deformation of the benzene ring in this compound.

It is worthy of note that Fries himself, who performed these experiments in order to compare benzimidazole with naphthalene, which he depicted by the Erlenmeyer formula, came very close to our picture of the structure of this heterocyclic compound. Fries believed, however, that in this case the properties of these two compounds ought to be fully similar, which was not the case of course. Whereas it is the α-positions that are most active in naphthalene [10], it is the 5 and 6 positions that are most active in benzimidazole. Failing to get to the bottom of this intricate complex of problems, Fries had to abandon this conception.

EXPERIMENTAL

Nitration of 2-methylbenzimidazole. 66 g of 2-methylbenzimidazole (0.5 mole) was carefully dissolved in 200 ml of conc. sulfuric acid in a beaker, using a stirrer. A nitrating mixture, consisting of 40 ml of nitric acid (sp. gr. 1.4) and 60 ml of sulfuric acid (sp.gr. 1.84), was added a drop at a time to the resulting solution, whose temperature was not allowed to rise above 25-30°. Fifteen to twenty minutes after this addition was complete the nitro mass was carefully poured into cold water (1 liter), and 160 ml of 50% nitric acid was added to the resulting solution. The white needles of 5-nitro-2-methylbenzimidazole nitrate that settled were filtered out after the solution had fully cooled, pressed out well, washed with small portions of ice water two or three times, suction-filtering the needles thoroughly each time, and dried. This yielded 108-112 g of product, representing about 90% of the theoretical.

Careful treatment of an aqueous solution of this nitrate with ammonia yielded free 5-nitro-2-methylbenzimidazole, with a m.p. of 219°. The free base need not be isolated, however, as the synthesized nitrate can be employed for the second nitration.

This was done by dissolving 50 g of the 5-nitro-2-methylbenzimidazole nitrate in 50 ml of conc.sulfuric acid, adding 100 ml of nitric acid (sp.gr. 1.52), and refluxing for one hour. The mass was then poured out into 500 ml of water containing ice, and the slightly soluble nitrate was filtered out. Some more of the product (2-5 g) could be recovered as a base from the mother liquor by neutralizing it with ammonia. All the product was converted into a base, carefully neutralizing its solution in 250 ml of water with ammonia and filtering after it had cooled. The 5,6-dinitro-2-methylbenzimidazole was separated from the initial 5-nitro-2-methylbenzimidazole by making use of the very sparing solubility of the hydrochloride of the former in aqueous hydrochloric acid solutions. This was done by dissolving the synthesized base in 250 ml of boiling water, adding hydrochloric acid a drop at a time, using no excess, filtering the solution, and then adding an equal volume of conc.hydrochloric acid to it. This precipitated the hydrochloride of the dinitroproduct, which was filtered out and dried. The yield totaled 45 g, or 83% of the theoretical.

Evaporating the hydrochloric mother liquor yielded a small quantity of a product that proved to be 5-nitro-2-methylbenzimidazole after it was purified.

5,6-Diamino-2-methylbenzimidazole. 30 ml of conc.hydrochloric acid and 20 g of granulated tin were placed in a small flask. Then 10 g of 5,6-dinitro-2-methylbenzimidazole hydrochloride was gradually added portionwise. The addition of each portion was accompanied by a violent reaction and the evolution of considerable heat. After addition was complete, the mass was heated for another 5-10 minutes until the solution had the color of strong tea. It was then decanted from the beaker containing the tin residue, the double tin salt of the reduction product settling out as the solution cooled. The salt was filtered out, squeezed out well to free it of the mother liquor, and dissolved in water, the tin being thrown down by passing a current of hydrogen sulfide through the solution. The mother liquor was evaporated to dryness in an evaporating dish on a water bath. This yielded 7 g of the dihydrochloride of 5,6-diamino-2-methyl-benzimidazole (approximately 80% of the theoretical) as a brownish powder that was excellently soluble in water. The diamine could be recovered from the solution as elongated sand-colored needles by carefully adding ammonia to a conc.aqueous solution of its hydrochloride and rubbing with a glass rod. The free diamine was also rather freely soluble in water, and particularly so in aqueous ammonia and alkalies, though it oxidized with extraordinary ease. This made working with it highly inconvenient.

Condensing 5,6-diamino-2-methylbenzimidazole with organic acids. Condensation was always effected by heating 2.35 g (0.01 mole) of the diamine dihydrochloride with 0.01 mole of the organic acid in 5 ml of 15% hydrochloric acid to 180° in sealed tubes for one hour. The reaction mass was then diluted with water and treated with ammonia, the condensation product being filtered out, washed with water, and then purified.

a) Condensation with formic acid yielded 1.5 g of methyldiimidazolo-1,2,4,5-benzene (VI), or 85% of the theoretical yield. The product was purified by dissolving it in water containing acetic acid, boiling with activated charcoal, and precipitating it from the hot solution with ammonia. M.p. 388-390°. A white, finely acicular product, freely soluble in aqueous mineral acids and acetic acid, sparingly soluble in most solvents. Its hydrochloride can be precipitated from an aqueous solution by acetone or by a large excess of conc.hydrochloric acid.

b) Condensation with acetic acid yielded 1.5 g of dimethyldiimidazolo-1,2,4,5-benzene (VII) —80% of the theoretical yield. The product was refined like the preceding one. M.p. 438-439°. Its properties resembled those of the preceding compound, but its hydrochloride was salted out from solution by hydrochloric acid somewhat more easily.

c) Condensation with benzoic acid yielded 1.5 g of methylphenyldiimidazolo-1,2,4,5-benzene (VIII) — 60% of the theoretical yield. The product was excellently refined as its hydrochloride, which crystallized from water containing hydrochloric acid as minute white needles.

0.1809 g subs.: 0.1602 AgCl. 0.1107 g subs.: 16.5 ml N_2 (16°, 760 mm). 0.1483 g subs.: 22.2 ml N_2 (20°, 770 mm). Found %: N 17.5, 17.8; Cl 21.92. $C_{15}H_{12}N_4 \cdot 2HCl$. Calculated %: N 17.45; Cl 22.1.

d) Condensation with phenylacetic acid yielded 2 g of methylbenzyldiimidazolo-1,2,4,5-benzene (IX) — approximately 77% of the theoretical yield. The substance was purified by crystallizing its dihydrochloride from water, being secured as minute white needles.

0.1070 g subs.: 14.75 ml N_2 (12°, 760 mm). 0.2212 g subs.: 0.1875 g AgCl. 0.1476 g subs.: 0.1252 g AgCl. Found %: N 16.55; Cl 20.95, 21.18. $C_{16}H_{14}N_4 \cdot 2HCl$. Calculated %: N 16.73; Cl 21.2.

e) Condensation with hydrocinnamic acid yielded 2 g methyl- β -phenylethyldimidazolo-1,2,4,5-benzene (X) — approximately 73% of the theoretical yield. The product was purified as its dihydrochloride, as in the preceding experiment.

0.1294 g subs.: 17.4 ml N_2 (12°, 760 mm). 0.1523 g subs.: 0.1251 g AgCl. 0.1400 g subs.: 0.1145 g AgCl. Found %: N 16.1; Cl 20.3, 20.25. $C_{17}H_{16}N_4 \cdot 2HCl$. Calculated %: N 16.05; Cl 20.35.

f) Condensation with 2-phenylbenzimidazole-5-carboxylic acid yielded 2 g of a derivative of diimidazolo-1,2,4,5-benzene (XI), which was purified from water as a salt containing three molecules of hydrochloric acid. It is very difficult to filter solutions of this salt.

0.1354 g subs.: 19.9 ml N_2 (18°, 773 mm). 0.1530 g subs.: 0.1378 g AgCl.
Found %: N 17.55; Cl 22.3. $C_{22}H_{16}N_6 \cdot 3HCl$. Calculated %: N 17.75; Cl 22.5.

Nitration of benzimidazole. The benzimidazole was nitrated to a 5-nitro derivative, and the latter was recovered as a nitrate after the mass had been poured into water by procedures that were fully analogous to those described for 2-methylbenzimidazole. The nitration product yield was approximately 95% of the theoretical. The second nitro group was added by refluxing 47 g of the nitrobenzimidazole nitrate for two hours in a solution of 94 ml of nitric acid (sp.gr. 1.52) and 49 ml of sulfuric acid (sp.gr. 1.84). Then the mass was poured into 500 ml of water containing ice, and the precipitated nitrate was filtered out. The product was converted into a base by carefully reacting an aqueous solution of the nitrate with ammonia, the base being recrystallized several times from water, yielding needles that fused, though not sharply, at 186°. The yield was 23 g. or 53% of the theoretical. The mother liquors probably contain nothing but a mixture of the initial product and the same dinitro product, since evaporation and numerous crystallizations of these liquors yielded very minute quantities of both of these compounds. The substance with an unsharp m.p. of 186° was analyzed.

0.1078 g subs.: 25.4 ml N_2 (24°, 764 mm). Found %: N 27.2. $C_7H_4N_4O_4$. Calculated %: N 26.9.

5,6-Diaminobenzimidazole. 25 g of granulated tin and 40 ml of conc. sulfuric acid were placed in a small, round-bottomed flask, and 8 g of the dinitro product with a m.p. of 186° was added portionwise. The reaction was very violent. As the resulting solution cooled, the double tin salt settled; it was filtered out and decomposed with hydrogen sulfide, the filtrate being evaporated to dryness on a water bath. This yielded 5.4 g of the diamine dihydrochloride as heavy brown crystals. We were unable to purify the product or convert it into a base because of its extremely high oxidizibility. Determination of the chlorine in the crude product yielded the following results:

0.1025 g subs.: 0.1340 g AgCl. Found %: Cl 32.25. $C_7H_8N_4 \cdot 2HCl$. Calculated %: Cl 32.1.

Condensation of 5,6-diaminobenzimidazole with organic acids. The condensation was always effected with 0.01 moles of the initial substances, as described in the preceding instances.

a) Condensation with formic acid yielded 1.2 g of diimidazolo-1,2,4,5-benzene, or 76% of the theoretical. The product was purified by dissolving it in hot water containing acetic acid, boiling the solution with activated charcoal, and precipitating with ammonia. Minute white needles with a m.p. of approximately 360°, freely soluble in dilute acids and very sparingly soluble in most organic solvents.

b) Condensation with acetic acid yielded 1.2 g of methyldimidazolo-1,2,4,5-benzene (VI), or approximately 70% of the theoretical. The product was purified as in the preceding instance. Its properties and its mixed melting point indicated that it was the same as the product previously prepared from 5,6-diamino-2-methylbenzimidazole and formic acid.

c) Condensation with benzoic acid yielded 1.2 g of phenyldiimidazolo-1,2,4,5-benzene (XV), or approximately 51% of the theoretical. The product was purified as its dihydrochloride, which crystallized satisfactorily from water as white needles.

0.1310 g subs.: 20.5 ml N_2 (20°, 760 mm). 0.1425 g subs.: 0.1335 g AgCl. 0.1913 g subs.: 0.1801 g AgCl. Found %: N 18.3; Cl 23.19, 23.23. $C_{14}H_{10}N_4 \cdot 2HCl$. Calculated %: N 18.25; Cl 23.35.

d) Condensation with phenylacetic acid yielded 1.7 g of benzyldiimidazolo-1,2,4,5-benzene (XVI), the yield being about 69% of the theoretical. The product was purified as its dihydrochloride by crystallization from water.

0.1010 g subs.: 15 ml N_2 (20°, 770 mm). 0.1159 g subs.: 0.1025 g AgCl. 0.1031 g subs.: 0.0911 g AgCl. Found %: N 17.53; Cl 21.9, 21.85. $C_{15}H_{12}N_4 \cdot 2HCl$. Calculated %: N 17.45; Cl 22.1.

e) Condensation with β-phenylpropionic acid yielded 1.5 g of β-phenylethyldiimidazolo-1,2,4,5-benzene (XVII). The product was purified as its dihydrochloride by crystallization from water.

0.1073 g subs.: 14.9 ml N_2 (14°, 760 mm). 0.1153 g subs.: 0.099 g AgCl. Found %: N 16.65; Cl 21.2. $C_{16}H_{14}N_4 \cdot 2HCl$. Calculated %: N 16.73; Cl 21.2.

f) Condensation with 2-phenylbenzimidazole-5-carboxylic acid yielded 1.7 g of the derivative (XVIII), which could be purified by crystallizing the trihydrochloride of that compound from water.

0.1001 g subs.: 15.7 ml N_2 (20°, 764 mm). 0.0609 g subs.: 0.0566 g AgCl. Found %: N 18.38; Cl 22.97. $C_{21}H_{14}N_6 \cdot 3HCl$. Calculated %: N 18.28; Cl 23.18.

SUMMARY

An investigation of the nitration of benzimidazole derivatives has indicated that this compound cannot be regarded merely as a benzene that contains two substituents in an ortho position to each other. This 2-ring system possesses distinctly specific properties, namely, high reactivity of the 5 and 6 positions and very weak conjugation between these positions. These specific peculiarities of benzimidazole may be attributed to the deformation of the benzene ring caused by the imidazole group condensed with it.

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## IV. THE CHEMICAL PROPERTIES OF DERIVATIVES OF 1,2,4,5-DIIMIDAZOLOBENZENE

L. S. Efros

In our preceding report [1] we set forth the hypothesis that the specific peculiarities of benzimidazole and its derivatives, manifested during nitration, are caused by the extensive impairment of the symmetry of the benzene ring in these compounds. This impairment of symmetry, due, most likely, to the attraction of electrons by the imidazole ring, results in the formation of double linkages between the 4-5 and the 6-7 carbon atoms in the benzene ring, while the bond between the 5 and 6 carbon atoms approaches the nature of a single bond (A).

(A)
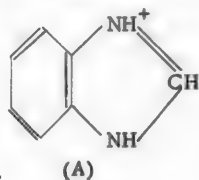
We thought that it would be of interest to make a study of the properties of the derivatives of 1,2,4,5-diimidazolobenzene (I), described previously [1], by way of obtaining further confirmation of the existence of this deformation of the benzene ring.

In a symmetrical molecule of these compounds the effect of two imidazole groups upon the double bonds of the central benzene ring ought to produce considerable unsaturation at the 3 and 6 positions, so that the state of the central benzene ring in Type (I) compounds ought to resemble that of anthracene, while the 3 and 6 positions ought to be like the meso position of the latter.

The most characteristic property of anthracene and its derivatives is the ability of these compounds to be oxidized to the corresponding anthraquinones fairly easily; we therefore commenced our research with an investigation of derivatives of diimidazolobenzene (I). We found that these compounds actually are oxidized fairly smoothly by a chromic acid mixture, resulting in nearly quantitative yields of the respective derivatives of 1,2,4,5-diimidazolo-3,6-benzoquinone. Thus, by oxidizing unsubstituted 1,2,4,5-diimidazolobenzene with chromic acid in boiling 45-50% sulfuric acid we secured a very high yield of the corresponding quinone (II), the disulfate of which settled out of the reaction mass as well-formed lemon-yellow needles.

(I)

(II)

(III)

(IV)
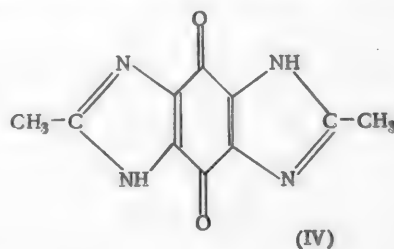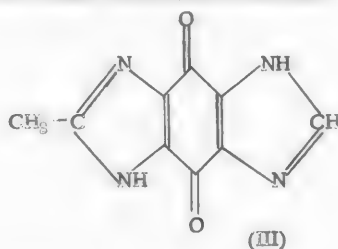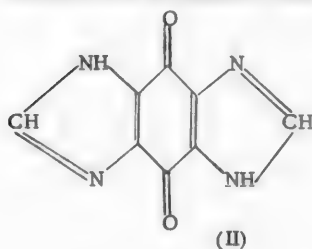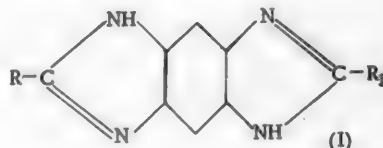
Similarly, oxidizing the methyl and dimethyl derivatives of diimidazolobenzene yielded the sulfates of the corresponding quinones (III) and (IV), the properties of which were very much like those of the quinone (II), the only difference being their somewhat lower solubility in acids.

Compounds of similar structure were also readily synthesized by oxidizing the methylphenyl (V) and methyl-β-pyridyl (VI) derivatives of diimidazolobenzene: (see top of next page)

Oxidation of methylbenzyldiimidazolobenzene (VII) was somewhat more difficult, the methylene group in the side chain being likewise oxidized, to judge by the high consumption of the oxidant and the elementary composition of the end product, the resulting compound probably having the composition of (VIII).

(V)

(VI)
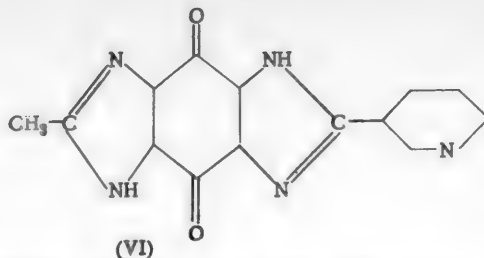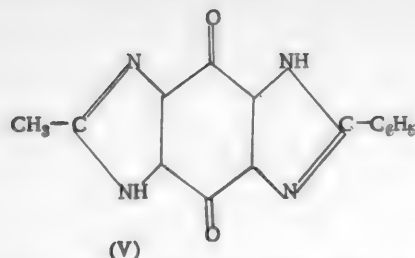
The sulfates or dihydrochlorides of all these compounds are lemon-yellow and are asymmetrical, their color being somewhat deeper than that of symmetrical substituted derivatives. As might have been expected, the basicity of the imidazole groups in these compounds is very greatly weakened by the proximity of the carbonyl groups, the sulfates and hydrochlorides referred to above being hydrolyzed even by traces of moisture, as in 96% alcohol. At first we get bright-red monoacid salts, one of which, constituting the compound (V), we managed to isolate in the chemically pure state. Further hydrolysis converts these salts into free quinone bases. In the case of the compounds (II), (III), (IV), and (VIII) these bases are various shades of orange-yellow, the asymmetrical compounds (V) and (VI) being colored violet-red and red respectively.

All these quinones dissolve in aqueous solutions of caustic alkalies, producing violet-blue solutions, from which the alkaline salts of the respective derivatives can be crystallized out by adding an excess of alkali, though mere chilling suffices in the case of the compound (V). We succeeded in purifying the potassium salt of the compound (V) by crystallizing it from water; it was converted thereby into a monometallic salt, probably due to partial hydrolysis, consisting of lustrous dark-green needles. When alkaline solutions of the quinones are reacted with hydrosulfite, they are decolorized as the result of the formation of leuco compounds, with the probable structure of (B).

(VII)

(VIII)

(B)
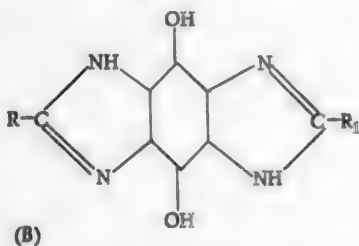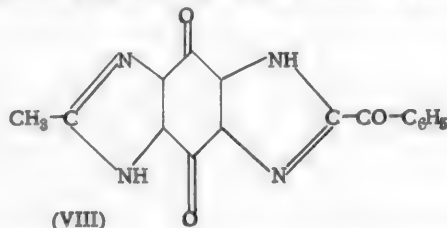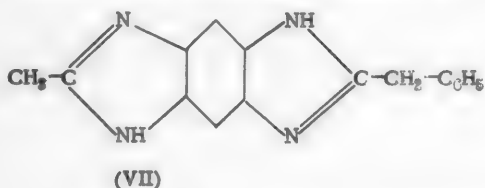
These colorless solutions are readily oxidized by atmospheric oxygen, their original violet-blue color being restored.

All the foregoing compels us to conclude that 1,2,4,5-diimidazolobenzene and its derivatives behave like anthracene in an oxidation reaction, as we had expected, readily producing derivatives of diimidazolobenzoquinone, an unusual analog of anthraquinone.

Extending our comparison of diimidazolobenzene (I) with anthracene to other reactions, we undertook an investigation of the chlorination, bromination, and nitration of these compounds. As we know, anthracene can be chlorinated and brominated very readily, the reaction immediately yielding 9,10-dihalogen derivatives [2]. We readily succeeded in chlorinating diimidazolobenzene as well as its methyl, dimethyl, and phenylmethyl derivatives by passing chlorine through solutions of these compounds in dilute hydrochloric acid in the cold. The chlorination products, the dichloro derivatives (IX), (X), (XI), and (XII), which were much less soluble in water, were crystallized from the solution as hydrochlorides: (see top of next page).

The location of the chlorine atoms in these compounds was established by oxidizing these substances with a chromic acid mixture. Chlorine was split out quantitatively in every instance, yielding the previously described quinones (II), (III), (IV), and (V). This transformation of the chloro derivatives upon oxidation indicates how extraordinarily closely these substances are related to anthracene, since such reactions are highly typical of the latter [3].

The introduction of chlorine atoms into diimidazolobenzene derivatives greatly diminishes the basicity of these compounds. The dihydrochlorides of the substances (IX), (X), and (XI), which are freely soluble in cold water,

(IX)   (X)   (XI)

(XII)
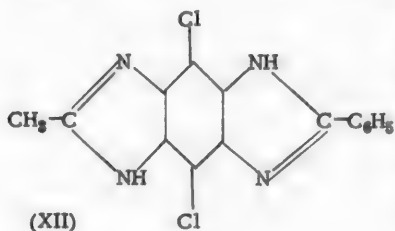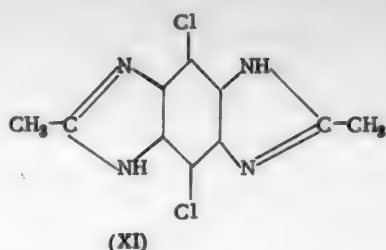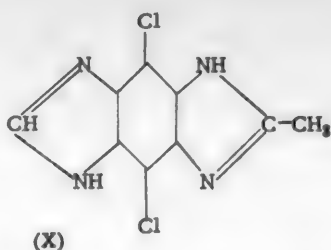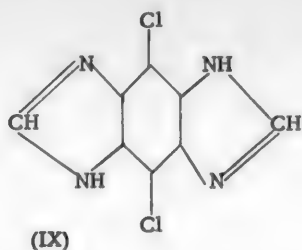
hydrolyze when heated, the respective bases settling out. As for the compound (XII), only its monoacid salt is stable.

The derivatives of diimidazolobenzene are likewise readily brominated when they are agitated with bromine in an aqueous 3% sulfuric acid solution. The bromo derivatives settle out, being purified later by crystallization from dilute hydrochloric acid. This yielded the following derivatives:

(XIII)   (XIV)   (XV)
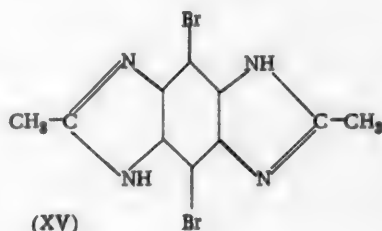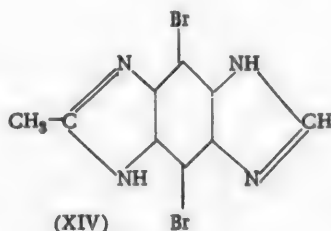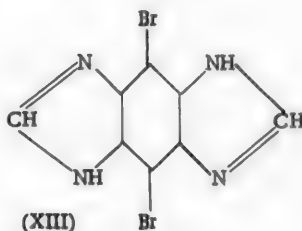
Here, too, the position of the bromine atoms was established by oxidizing these substances to convert them into the quinones (II), (III), and (IV) that contained no halogen. The properties of the bromo derivatives greatly resembled those of the chloro substitution derivatives already described, so that we shall not dwell upon them at this point.

The derivatives of diimidazolobenzene (I) are readily nitrated in sulfuric acid under the usual conditions. We were able to isolate the nitro derivatives by pouring the nitro mass into water, carefully neutralizing with ammonia, and then crystallizing from alcohol. This yielded nitro derivatives with the following structures:

(XVI)   (XVII)   (XVIII)
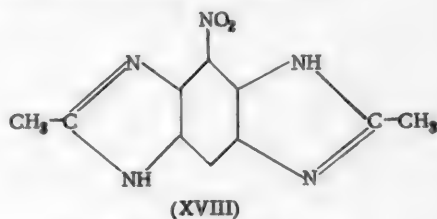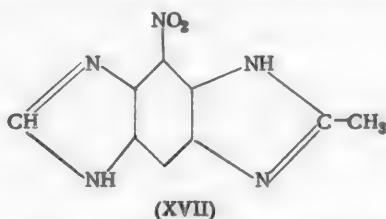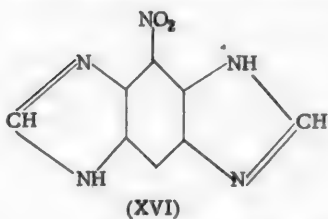
They were all bright-yellow substances that dissolved in dilute mineral acids, producing colorless solutions. The effect of the nitro group increases the acidic properties of the imino groups in these compounds, so that they are fairly freely soluble in ammonia and soda, in addition to caustic alkalies, thus differing from the initial products.

Since we know that anthracene and some of its derivatives can also yield meso dinitro derivatives [4] under certain conditions, we tried to introduce another nitro group into the synthesized substances, but we did not succeed, even when using the most severe conditions. This evidently means that the effect of the nitro group, which prevents the second substituent from entering at the para position, is much stronger in derivatives of diimidazolobenzene than in anthracene.

It is apparently this same circumstance that is responsible for the fact that our attempt to oxidize the nitro compounds into the previously described quinones likewise met with failure. No reaction took place; we recovered the original products unchanged in very case.

The experimental data cited indicate that our prediction of the chemical similarity between 1,2,4,5-diimidazobenzene and anthracene is correct. This also confirms our hypothesis of the deformation of the benzene ring by the imidazole group, upon which this theoretical conclusion was founded.

EXPERIMENTAL

I. Oxidation of Derivatives of 1,2,4,5-Diimidazolobenzene

a) **Dimethyl-1,2,4,5-diimidazolo-3,6-benzoquinone.** 5 grams of dimethyl-1,2,4,5-diimidazolobenzene was dissolved in 70 ml of 40% sulfuric acid and heated to boiling, and 7.5 g of chromic acid was gradually added. When the reaction was over (it did not set in at once, but later was fairly violent), the lustrous crystals of the quinone disulfate began to settle out of the still hot solution. They were filtered out on a glass filter, washed first with a small amount of cold 40% sulfuric acid and then with absolute alcohol and ether, and then dried. The yield totaled 9.5 g of beautiful light-yellow crystals.

The quinone sulfate could be readily crystallized from 40% sulfuric acid, as elongated light needles, lemon-yellow in color, which were washed with absolute alcohol and ether to eliminate the sulfuric acid mother liquor (aqueous alcohol hydrolyzed the salt). The percentage of sulfuric acid in the salt was determined by analysis, a sample being dissolved in water containing hydrochloric acid and the $SO_4^=$ precipitated with barium chloride.

0.1030 g, 0.1045 g substance: 0.1168 g, 1.1181 g $BaSO_4$. Found %: H_2SO_4 47.56, 47.45. $C_{10}H_8O_2N_4 \cdot 2H_2SO_4$. Calculated %: H_2SO_4 47.57.

The quinone salt is hydrolyzed even by traces of water, first yielding a bright-red product, which turns orange-yellow upon further treatment with water. This was a quinone base, which was purified by repeated washings with water, alcohol, and ether, and then dried to constant weight. It was soluble neither in water nor in organic solvents, though it did dissolve in 5-10% sulfuric acid, producing light-yellow solutions.

The quinone was also soluble in caustic alkalies, producing violet solutions. Adding an excess of alkali decolorized the solution, the quinone salts crystallizing out as dark needles. Alkaline solutions of the quinone were decolorized when hydrosulfite was added. When the solution was shaken up with air, the color reappeared. The melting point of the base lay above 400°.

0.1055 g substance: 0.2130 g CO_2, 0.0371 g H_2O. 0.1440 g, 0.1069 g substance: 32.6 ml, 24.2 ml N_2 (22°, 752 mm). Found %: C 55.4; H 3.9; N 25.92, 25.91. $C_{10}H_8O_2N_4$. Calculated %: C 55.5; H 3.7; N 25.92.

b) **Methyl-1,2,4,5-diimidazolo-3,6-benzoquinone.** 1.2 grams of methyl-1,2,4,5-diimidazolobenzene (cf [1] for its synthesis) was dissolved in 15 ml of 40% sulfuric acid, and 1.8 g of chromic acid was added to the boiling solution. When the reaction was over and the solution cooled down, the mass solidified due to the settling out of crystals of the quinone disulfate. The product was filtered out and washed with alcohol. The salt yield totaled 1.2 g. In this case the mother liquor still contained an appreciable quantity of the quinone, which we managed to recover by diluting with water and carefully neutralizing with ammonia. This yielded another 0.5 g of the quinone base. The two products were combined together and purified by crystallization from a mixture of equal volumes of 40% sulfuric acid and alcohol. The light and elongated light-yellow needles that settled out, were washed with absolute alcohol and ether and dried, as in the preceding experiment. The percentage of sulfuric acid in the quinone salt was determined by analysis, as in the preceding test.

0.1003 g substance: 0.1175 g $BaSO_4$. Found %: H_2SO_4 49.20. $C_9H_6O_2N_4 \cdot 2H_2SO_4$. Calculated %: H_2SO_4 49.24

The quinone base was obtained by boiling the recrystallized salt with water, the orange-yellow precipitate being filtered, washed with water, alcohol, and ether, and dried to constant weight. The quinone did not melt when heated to 400°. It was insoluble in organic solvents, though it did dissolve in aqueous caustic alkalies, producing violet-blue solutions that were decolorized by hydrosulfite.

0.1026 g substance: 25.5 ml N_2 (24°, 740 mm). Found %: N 27.81. $C_9H_6O_2N_4$. Calculated %: N 27.72.

c) **1,2,4,5-Diimidazolo-3,6-benzoquinone.** This was prepared exactly like the quinones described above. In this case, however, it is best to isolate it from the reaction mass as a base, owing to the high solubility of its sulfate in water. This was done by diluting the reaction mass with water and partially neutralizing it with ammonia. The precipitated base was filtered out and washed well with water, alcohol, and ether. One gram of

diimidazolobenzene yielded approximately 1 g of the quinone base. The color, solubility, and properties of this product hardly differ from those of the compounds described previously.

0.1012 g substance: 0.1892 g CO_2, 0.0201 g H_2O. 0.1297 g substance: 33.6 ml N_2 (22°, 752 mm). Found %: C 50.93; H 2.20; N 29.66. $C_8H_4O_2N_4$. Calculated %: C 51.06; H 2.13; N 29.79.

d) Methylphenyl-1,2,4,5-diimidazolo-3,6-benzoquinone. 2.6 grams of methylphenyl-1,2,4,5-diimidazolo-benzene disulfate (cf. [1] for its synthesis) was dissolved by heating it in 60 ml of 50-60% sulfuric acid, and a solution of 1.5 g of chromic acid in 2-3 ml of water was added. Chilling resulted in crystallizing out a minute quantity of the sulfate of the original product, which was filtered out and converted into the hydrochloride [1]. This yielded approximately 0.5 g of this salt.

The green mother liquor was diluted with 4 times its volume of water, which caused it to turn red. It was neutralized with ammonia and then with sodium acetate until it no longer reacted acid with Congo red, after which the precipitated violet-red reaction product was filtered out and washed well with water. The product was purified by recrystallizing it from 200 ml of dilute hydrochloric acid, from which it was recovered as well-formed, bright-red needles of the monohydrochloride. They were thoroughly washed with absolute alcohol and ether, and then dried. The yield was 1.5 g.

0.1024 g substance: 0.0482 g AgCl. Found %: Cl 11.65. $C_{15}H_{10}O_2N_4 \cdot HCl$. Calculated %: Cl 11.29.

When the mother liquor, which contained hydrochloric acid, was not washed out of the monohydrochloride before the latter was dried, the salt gradually turned into the light-yellow sulfate. The latter salt was also analyzed.

0.1359 g, 0.1366 g substance: 0.1128 g, 0.1131 g AgCl. Found %: Cl 20.5, 20.5 $C_{15}H_{10}O_2N_4 \cdot 2HCl$. Calculated %: Cl 20.25.

Both salts of the quinone in question were somewhat soluble in cold water, but they hydrolyzed when only gently heated, a finely crystalline, more deeply colored quinone base settling out. It was filtered out, washed with water, alcohol, and ether, and then dried to constant weight.

0.1045 g substance: 0.2475 g CO_2, 0.0341 g H_2O. 0.1187 g substance: 20.8 ml N_2 (22°, 752 mm). Found %: C 64.5; H 3.62; N 20.07. $C_{15}H_{10}O_2N_4$. Calculated %: C 64.75; H 3.59; N 20.17.

The quinone base dissolved in caustic alkalies, producing a violet color; when these solutions were cooled, they were decolorized, the quinone salt crystallizing out in beautiful needles. This salt could be recrystallized from water, being obtained as large green needles.

e) Methyl-β-pyridyl-1,2,4,5-diimidazolo-3,6-benzoquinone. 1.7 grams of methyl-β-pyridyl-1,2,4,5-diimidazolobenzene was dissolved in 15 ml of concentrated sulfuric acid, the solution was diluted with 30 ml of water, and a solution of 3 g of chromic acid in 5 ml of water was added. When the vigorous reaction was over and the solution had cooled, the slight precipitate was filtered out, the solution being diluted with water to make 200 ml and then neutralized until its reaction was rather rigorously neutral. The resulting red precipitate of the quinone base was filtered out and washed with water, alcohol, and ether. The yield totaled 0.7 g (judging by the red color of the solution, part of the product was lost in the mother liquor). The product dissolved readily in dilute acids, producing yellow solutions, from which no quinone salt could be isolated. Heating in aqueous alkalies produced violet-blue solutions, from which a crystalline precipitate settled out upon cooling, the solutions being decolorized.

0.1032 g substance: 22.2 ml N_2 (15°, 750 mm). Found %: N 25.17. $C_{14}H_9O_2N_5$. Calculated %: N 25.09.

II. Chlorination and Bromination of 1,2,4,5-Dimidazolobenzene Derivatives

One gram of 1,2,4,5-diimidazolobenzene or of one of its derivatives was always dissolved in 50 ml of dilute hydrochloric acid, and gaseous chlorine was passed through the resultant solutions. White precipitates of the respective dichloro derivatives gradually separated as hydrochlorides. They were filtered out and crystallized several times from water containing hydrochloric acid.

a) The yield of 3,6-dichloro-1,2,4,5-diimidazolobenzene dihydrochloride totaled 1.5 g. White crystals, soluble in cold water and settling out when these solutions were heated, owing to hydrolysis. Adding hydrochloric acid produces dissolution, while an excess of the hydrochloric acid salts the substance out of the solution.

Determining the ionizing chlorine: 0.1012 g, 0.1015 g substance: 0.0971 g, 0.0973 g AgCl. Found %: Cl 23.70, 23.68. $C_8H_4N_4Cl_2 \cdot 2HCl$. Calculated %: Cl 23.67.

Determining total chlorine: 0.1025 g, 0.1073 g substance: 0.1960 g, 0.2055 g AgCl (Carius).
Found %: Cl 47.28, 47.25. $C_9H_6N_4Cl_4$. Calculated %: Cl 47.33.

b) The yield of methyl-3,6-dichloro-1,2,4,5-diimidazolobenzene hydrochloride was 1.5 g. It differed from the preceding product only in its poor solubility in water and particularly in dilute hydrochloric acid.

Determining the ionizing chlorine: 0.1100 g substance: 0.0997 g AgCl. Found %: Cl 22.4.
$C_9H_8N_4Cl_2 \cdot 2HCl$. Calculated %: Cl 22.6.

c) Dimethyl-3,6-dichloro-1,2,4,5-diimidazolobenzene dihydrochloride. 1.4 g yield. It differed from the preceding compounds only in its somewhat poorer solubility.

Determining the ionizing chlorine: 0.1068 g, 0.1157 g substance: 0.0935 g, 0.1005 g AgCl.
Found %: Cl 21.67, 21.5. $C_{10}H_8N_4Cl_2 \cdot 2HCl$. Calculated %: Cl 21.65

Determining the total chlorine: 0.1027 g, 0.1003 g substance: 0.1822 g, 0.1773 g AgCl (Carius).
Found %: Cl 43.71, 43.7. $C_{10}H_{10}N_4Cl_4$. Calculated %: Cl 43.29.

Part of the product was converted into a base by treating it with aqueous ammonia, the base being thoroughly washed with water and dried before analysis.

0.1004 g, 0.1001 g substance: 0.1119 g, 0.1110 g AgCl. Found %: Cl 27.55, 27.45. $C_{10}H_8N_4Cl_2$.
Calculated %: Cl 27.85.

d) Methylphenyl-3,6-dichloro-1,2,4,5-diimidazolobenzene hydrochloride. 1.1 g yield. The product dissolved with difficulty in water, slightly acidulated with hydrochloric acid, and differed from the preceding compounds in precipitating monohydrochloride.

Determining the ionizing chlorine: 0.0906 g substance: 0.0367 g AgCl. Found %: Cl 10.03.
$C_{15}H_{10}N_4Cl_2 \cdot HCl$. Calculated %: Cl 10.3.

Determining the total chlorine: 0.1055 g substance: 0.1279 g AgCl (Carius). Found %: Cl 30.01.
$C_{15}H_{10}N_4Cl_2$. Calculated %: Cl 30.13.

2) All the derivatives of diimidazolobenzene were brominated as follows: 0.005 mole of the original compound was dissolved in 50 ml of water, to which the necessary quantity of sulfuric acid was added. 1.6 grams of bromine was added to the resulting solution, and the whole was agitated vigorously. The bromination product soon settled out; it was filtered out and crystallized from water containing hydrochloric acid.

a) 3,6-Dibromo-1,2,4,5-diimidazolobenzene dihydrochloride.

Determining the ionizing chlorine: 0.1015 g, 0.1026 g substance: 0.0747 g, 0.0755 g AgCl. Found %:
Cl 18.20, 18.25. $C_8H_6N_4Br_2 \cdot 2HCl$. Calculated %: Cl 18.25.

Treating the product with aqueous ammonia converted it into a base, which was thoroughly washed with water and dried, after which it was analyzed.

0.1002 g, 0.1076 g substance: 0.1189 g, 0.1279 g AgBr. Found %: Br 50.65, 50.67.
$C_8H_4N_4Br_2$. Calculated %: Br 50.63.

b) Methyl-3,6-dibromo-1,2,4,5-diimidazolobenzene dihydrochloride.

0.1007 g, 0.1101 g substance: 0.0716 g, 0.0782 g AgCl. Found %: Cl 17.58, 17.6. $C_9H_6N_4Br_2 \cdot 2HCl$.
Calculated %: Cl 17.61.

The bromine in the free base was determined by the Carius method:

0.0987 g, 0.0951 g substance: 0.1120 g, 0.1081 g AgBr. Found %: Br 48.3, 48.45. $C_9H_6N_4Br_2$.
Calculated %: Br 48.48.

c) Dimethyl-3,6-dibromo-1,2,4,5-diimidazolobenzene dihydrochloride.

0.0990 g, 0.0984 g substance: 0.0686 g, 0.0680 g AgCl. Found %: Cl 17.09, 17.07.
$C_{10}H_8N_4Br_2 \cdot 2HCl$. Calculated %: Cl 17.05.

The bromine in the free base was determined by the Carius method:

0.1087, 0.1008 g substance: 0.1201 g, 0.1101 g AgBr. Found %: Br 47.0, 46.45.
$C_{10}H_8N_4Br_2$. Calculated %: Br 46.51.

3) The chloro and bromo derivatives were oxidized and the quinones were isolated by about the same methods as those described in detail in Part (1) of the experimental section. The quinones synthesized from the halogen derivatives were identified with those synthesized previously by their properties and qualitative reactions. Moreover, we checked the absence of halogen in these compounds by a Beilstein test in every case. All of these tests were negative. The oxidation of the dibromo derivative of dimethyldiimidazolobenzene is described below by way of example.

0.6 gram of the dibromide was dissolved in 10 ml of concentrated sulfuric acid and then diluted with 15 ml of water. 0.5 gram of chromic acid was added to the solution, which was then heated to boiling. The odor of the liberated bromine became clearly perceptible and the oxidation reaction proceeded. As the solution cooled the quinone sulfate settled out; it was purified as described above (see Ia). It contained no halogen, and its properties indicated its identity with the compound (IV) described previously.

III. Nitration of Diimidazolobenzene Derivatives.

0.01 gram of the original diimidazolobenzene derivative was dissolved in 12 ml conc. sulfuric acid and a nitrating mixture of 0.5 ml of nitric acid (sp.gr. 1.48) and 1 ml of sulfuric acid was added a drop at a time at 15-20°, with mechanical stirring. After the mass had stood for half an hour, it was poured into 100 ml of water and carefully neutralized with ammonia. Bright-yellow products settled out; they were filtered out, thoroughly washed with water, and dried, after which it was crystallized from alcohol. The product yields approached the quantitative.

The synthesized substances were only very slightly soluble in water, freely soluble in aqueous solutions of mineral acids, producing colorless solutions, somewhat less soluble in acetic acid, freely soluble in caustic alkalies, and moderately soluble in ammonia. They settled out of solution as yellow needles at their isoelectric point. The melting point of the products lay above 360°.

a) Nitrodiimidazolobenzene (XVI).

0.0105 g substance: 29.3 ml N_2 (15°, 760 mm). 0.0955 g substance: 28.0 ml N_2 (16°, 760 mm).
Found %: N 34.60, 34.65. $C_8H_5O_2N_5$. Calculated %: N 34.48.

b) Nitromethyldiimidazolobenzene (XVII).

0.0982 g substance: 26.4 ml N_2 (16°, 770 mm) 0.0809 g substance: 22.1 ml N_2 (17°, 770 mm).
Found %: N 32.20, 32.55. $C_9H_7O_2N_5$. Calculated %: N 32.26.

c) Nitrodimethyldiimidazolobenzene (XVIII).

0.1175 g substance: 30.3 ml N_2 (24°, 774 mm). Found %: N 30.28. $C_{10}H_9O_2N_5$. Calculated %: N 30.30.

We attempted to nitrate these compounds further under varying conditions, but without success. For instance, 4 g of the nitro product (XVIII) was refluxed in a solution of 4 ml of concentrated sulfuric acid and 8 ml of nitric acid (sp. gr. 1.5) for three hours. The mass was poured into water and neutralized with ammonia. A yellow product settled out, which was filtered out and purified, proving to be the original compound. Refining yielded 3.5 g of the substance.

We attempted to oxidize these compounds by boiling them with a chromic acid mixture the sulfuric acid in which was raised as high as 70%. The oxidant was gradually consumed [1.5 g of chromic anhydride being taken per gram of the nitro product (XVIII)], but still the product was recovered unchanged.

SUMMARY

The hypothesis advanced in our preceding report [1] that the benzene ring is deformed by benzimidazole derivatives enabled us to draw the theoretical conclusion that 1,2,4,5-diimidazolobenzene and anthracene were chemically similar in the constitution of their central benzene rings. This conclusion has been confirmed by our experimental investigation of the chemical properties of diimidazolobenzene derivatives. In our research we have secured new derivatives of 1,2,4,5-diimidazolobenzene, as well as chloro, bromo, and nitro derivatives of 1,2,4,5-diimidazolobenzene.

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[4] Meisenheimer, Connerade, Ann., 330, 170 (1904).

THIAZOLIDINE-4-CARBOXYLIC ACID AND ITS DERIVATIVES

II. S-SUBSTITUTION DERIVATIVES OF CYSTEINE AND THEIR TRANSFORMATION INTO DERIVATIVES OF THIAZOLIDINE-4-CARBOXYLIC ACID

I. T. Strukov

In Report I we showed [1] that it is fairly easy to close the pyrrolidine ring, producing thiazolidine-pyrrolidine ring systems.

In the present research we endeavored to use this method to secure simple model compounds with a thiazolidine-β-lactam ring system by synthesizing 2-(α-phenyl-α-carbethoxymethyl)-thiazolidine-4-carboxylic acid [1] from 1-cysteine hydrochloride and ethyl formylphenylacetate (II) [2].

We were unable to close the β-lactam ring, however: no reaction took place when the compound (I) was heated to 100°, while carbon dioxide and hydrogen sulfide were given off at 150-160°. It was apparent that the foregoing method could not be employed in this instance. The same result was secured when 2-(α-phenyl-α-carbethoxymethyl)-thiazolidine-4-carboxylic acid was used. We therefore tried to saponify the ester group in (I) and then close the β-lactam ring. We found that saponifying it in an aqueous alcoholic solution with sodium hydroxide under mild conditions simultaneously ruptured the thiazolidine ring.
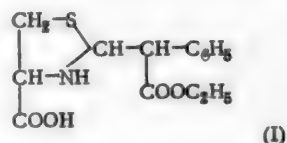
Preparation of 2-(α-phenyl-α-carboxymethyl)-thiazolidine-4-carboxylic acid (VII) by another method required formylphenylacetic acid (V), which we thought we could produce from its ester, but when we saponified ethyl formylphenylacetate under relatively mild conditions we got phenylacetic acid rather than formylphenylacetic acid. The formyl group proved to be unstable in the presence of an aqueous-alcoholic alkali.

We managed to prepare formylphenylacetic acid from ethyl formylphenylacetate, however, via the diethyl acetal of ethyl formylphenylacetate (III) and the diethyl acetal of formylphenylacetic acid (IV), by treating the latter with concentrated hydrochloric acid:
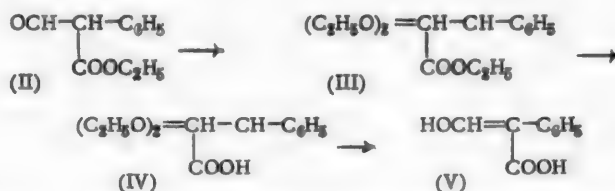
It was synthesized in the oxymethylene form. Oxymethylenephenylacetic acid is fairly stable in an acid medium, but is readily decomposed by an alkali, yielding phenylacetic acid.

When oxymethylenephenylacetic acid is condensed with 1-cysteine hydrochloride in methanol at room temperature, carbon dioxide is liberated and 2-benzylthiazolidine-4-carboxylic acid (VI) is produced, which readily hydrolyzes in water:
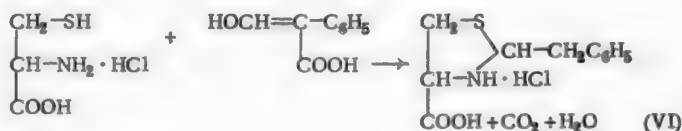
The same results were obtained when this reaction was carried out in pyridine. It was found that pyridine

breaks down oxymethylenephenylacetic acid very rapidly, forming phenylacetaldehyde and carbon dioxide. Hence, the cysteine reacts with the phenylacetaldehyde rather than with the oxymethylenephenylacetic acid, giving rise to the compound (VI). Only once were we able to prepare 2-(α-phenyl-α-carboxymethyl)-thiazolidine-4-carboxylic acid (VII): by condensing the diethyl acetal of formylphenylacetic acid with 1-cysteine hydrochloride.

$$CH_2-S$$
$$|\qquad\quad CH-CH-C_6H_5$$
$$CH-NH\qquad |$$
$$|\qquad\qquad COOH$$
$$COOH\qquad (VII)$$
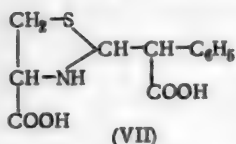
All attempts to repeat that experiment were unsuccessful, 2-benzylthiazolidine-4-carboxylic acid being secured every time.

Inasmuch as oxymethylenephenylacetic acid is fairly stable in an acid medium, we tried to condense it with dl-cysteine in concentrated hydrochloric acid at 0°. This yielded S-β-(α-phenyl-α-carboxy)-ethylenecysteine hydrochloride instead of the thiazolidine compound (VII); we isolated the free acid (VIII) from this hydrochloride.

Concentrated hydrochloric acid apparently blocks the primary amino group, which does not take part in the reaction.

$$CH_2-S-CH=C-C_6H_5$$
$$|\qquad\qquad\quad|$$
$$CH-NH_2\qquad COOH$$
$$|$$
$$COOH\qquad\qquad (VIII)$$
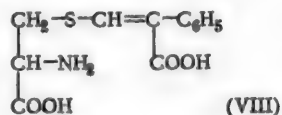
The reaction followed the same lines when ethyl formylphenylacetate and ethyl methoxymethylenephenylacetate (IX) were condensed with dl-cysteine. In both cases we secured the hydrochloride of S-β-(α-phenyl-α-carbethoxy)-ethylenecysteine (X), from which we isolated the free acid (XI):

$$CH_2-SH\qquad\qquad CH_3OCH=C-C_6H_5$$
$$|\qquad\qquad\qquad +\qquad\qquad\quad|$$
$$CH-NH_2\cdot HCl\qquad\qquad\quad COOC_2H_5$$
$$|$$
$$COOH\qquad\qquad\qquad (IX)$$

$$\qquad\qquad CH_2-S-CH=CH\overset{C_6H_5}{\underset{COOC_2H_5}{\big<}}$$
$$\longrightarrow\quad |$$
$$\qquad\qquad CH-NH_2\cdot HCl$$
$$\qquad\qquad |$$
$$\qquad\qquad COOH\qquad\qquad (X)$$

Ethyl formylphenylacetate exists in three tautomeric forms [3], though only the oxymethylene form can yield the compound (X). Hence the yield when ethyl methoxymethylenephenylacetate was used was about twice as high as when we used ethyl formylphenylacetate.

The S-substitution derivatives of cysteine, in which the sulfur is linked to a carbon atom that has a double bond, may be regarded as a tautomeric form of thiazolidine compounds, though we know of no instances of a conversion of thiazolidine compounds into S-substituted compounds. The physical and chemical properties of the S-substitution derivatives of cysteine differ greatly from those of the corresponding thiazolidine compounds: they are not oxidized by an iodine solution, they do not react with mercuric chloride in the cold, they form freely water-soluble salts wit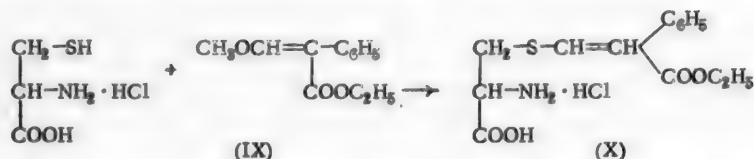h mineral acids, and their acetyl compounds have low melting points. The thiazolidine compounds described by Ratner and Clarke [4] and other authors behave differently. Compound (I), in particular, is oxidized by iodine and reacts with mercuric chloride to form a precipitate of a complex mercuric salt of cysteine and the formylphenylacetic ester, and its hydrochloride is readily hydrolyzed by water.

It is worthy of note that the aldehydic form of the formylphenylacetic ester can be secured in the pure state by oxidizing the thiazolidine compound (I) with iodine. This method of converting compounds that have two tautomeric forms — the aldehydic and the oxymethlenic — by transforming them into thiazolidine compounds may make it possible to isolate only the aldehydic form in the pure state.

In connection with the synthesis of S-substitution derivatives of cysteine the idea arose of trying to convert the compound (XI) into a compound with a seven-membered ring system (XII), in the expectation that a further shift of hydrogen from the nitrogen atom to the double bond would take place, yielding the thiazolidine-β-lactam ring system (XIII): (see top of next page).

According to Fisher [5] six-membered ring systems may be closed rather readily in an intramolecular reaction of the methyl esters of Δ-amino acids. Though closing the seven-membered rings of esters of ε-amino acids is much more difficult, testing this hypothesis was of extraordinary interest in solving problems involved in the synthesis of penicillin.

As a matter of fact, we obtained the thiazolidine compound (I) whenever we heated the sodium salt of S-β-(α-phenyl-α-carboethoxy)-ethylenecysteine or the free acid in pyridine. In an amino group that is not linked to hydrogen chloride, therefore, the hydrogen resumes its mobility and shifts to the double bond, resulting in closure of the thiazolidine ring. The same holds true of the carbomethoxy analog as in the compound (VIII), no thiazolidine compound is formed. Ratner and Clarke consider thiazolidine compounds to be in a state of

equilibrium with cysteine and the aldehyde.

$$CH_2-S-CH=C-C_6H_5$$
$$CH-NH_2 \quad COOC_2H_5$$
$$COOH$$
(XI)

$$CH_2-S \quad CH-CH-C_6H_5$$
$$CH-NH \quad COOC_2H_5$$
$$COOH$$
(I)

$$CH_2-S-CH=C-C_6H_5$$
$$CH-NH-CO$$
$$COOH$$
(XII)

$$CH_2S$$
$$CH-CH-C_6H_5$$
$$CH-N \quad CO$$
$$COOH$$
(XIII)
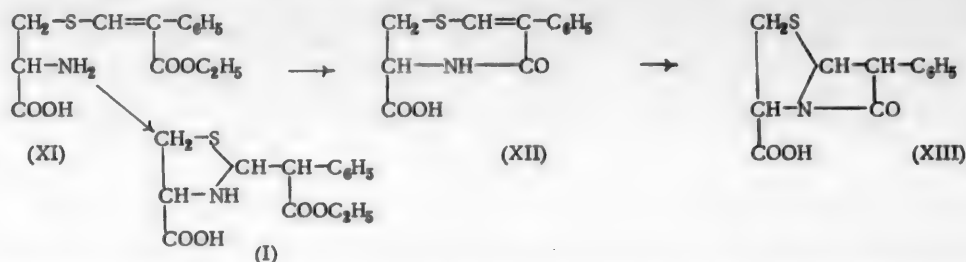
When thiazolidine compounds are acylated, the bonds between the sulfur and nitrogen atoms and the carbon atoms are stabilized, and the sulfur is not oxidized by iodine. We were able to saponify the acetyl compound (XIV) produced by acetylating 2-(a-phenyl-a-carbomethoxymethyl)-thiazolidine-4-carboxylic acid (I), obtaining 2-(a-phenyl-a-carboxymethyl-N-acetylthiazolidine-4-carboxylic acid (XV):

$$CH_2-S \quad CH-CH-C_6H_5$$
$$CH-N \quad COOCH_3$$
$$COOH \quad COCH_3$$
(XIV)

$$CH_2-S \quad CH-CH-C_6H_5$$
$$CH-N \quad COOH$$
$$COOH \quad COCH_3$$
(XV)
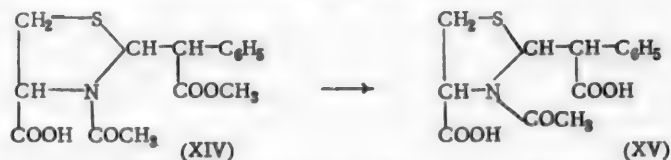
Stabilization of thiazolidine compounds by acylating an amino group is an extremely interesting problem in theoretical chemistry. It is hard to judge the strength or the stability of the bonds in most organic molecules. When we compare the compounds (XI) and (XIV), we can hardly say that the bond between the sulfur and the carbon atom in the ethylene group in (XI) is more stable than in the compound (XIV). But when thiazolidine compounds are acylated, the energy expended in binding the nitrogen atom to the CH_3CO group is taken from the nitrogen, thus reinforcing the bond between the sulfur and carbon atoms in the compound (XIV).

As for the instability of oxymethylenephenylacetic acid, it must be assumed that it is related to the mobility of the hydrogen in the oxymethylene group, which results in this compound's existing in several tautomeric forms. This also gives rise to the differing nature of its cleavage: it is converted into phenylacetic acid by the action of an alkali, while dissolution in pyridine converts it into phenylacetaldehyde and carbon dioxide.

EXPERIMENTAL

2-(a-Phenyl-a-carbethoxymethyl)-thiazolidine-4-carboxylic acid. 10 grams of l-cysteine hydrochloride, 12 g of ethyl formylphenylacetate, and 2 ml of water were placed in a 50-ml round-bottomed flask and heated and stirred for 15 minutes on a boiling water bath, producing a transparent, light-yellow solution. The solution was gradually poured into 250 ml of water, and 46 ml of an 8% solution of sodium bicarbonate was slowly added. The next day the precipitate was filtered out, washed with water, and dried in a vacuum desiccator. Then it was washed with ether and recrystallized from alcohol. Very thin needles with an m.p. of 168-169° (with decomposition).

8.239 mg substance: 0.337 ml N_2 (21.5°, 757 mm). 7.735 mg substance: 0.308 ml N_2 (19°, 758 mm). Found %: N 4.64, 4.71. $C_{14}H_{17}O_4NS$. Calculated %: N 4.74.

The hydrochloride of the 2-(a-phenyl-a-carbethoxymethyl)-thiazolidine-4-carboxylic acid was prepared by passing anhydrous hydrogen chloride through an ether solution of the acid; m.p. 163-165° (with decomposition). 2 grams of the acid was dissolved in 20 ml of water, a solution of sodium bicarbonate was gradually added, and the solution was treated with an 0.1N solution of iodine until the light-yellow coloring persisted for several seconds. The solution was treated with three times its weight of ether, the ether extract was dried with sodium sulfate, the ether was driven off, and the residual oil was distilled in vacuo. B.p. 135-140° at 10 mm. The oil crystallized, the crystals being washed with gasoline. This yielded flakes with an m.p. of 70-71°, which exhibited a silver mirror reaction. They were identified as the keto form of ethyl formylphenylacetate, synthesized by Wislicenus [2].

After the ether extraction l-cysteine was recovered from the aqueous solution as regular hexagonal crystals.

<u>Methyl ester of 2-(a-phenyl-a-carbethoxymethyl)-thiazolidine-4-carboxylic acid</u>. 5 grams of the acid was dissolved in 50 ml of methanol and the chilled solution was saturated with hydrogen chloride. The next day the solvent and the hydrogen chloride were driven off in vacuo, and the remaining thick yellow oil was dissolved in water, the resulting solution being alkalinized and the substance that separated out being extracted with ether. The extract was washed with water and dried with anhydrous sodium sulfate, the ether being driven off and the residual oil being dried in vacuo. It weighed 4.7 g. The yellow oil was freely soluble in alcohol, ether, acetone, and benzene.

7.299 mg substance: 0.285 ml N_2 (19°, 741.4 mm). Found %: N 4.45. $C_{15}H_{19}O_4NS$. Calculated %: N 4.53.

<u>2-(a-Phenyl-a-carbethoxymethyl)-N-acetylthiazolidine-4-carboxylic acid</u>. 2 grams of 2-(a-phenyl-a-carbethoxymethyl)-thiazolidine-4-carboxylic acid was dissolved in 5 ml of pyridine, and 1 ml of acetic anhydride was added. One hour later the mass was gradually poured into 20 ml of 20% sulfuric acid. The resulting precipitate was filtered out, washed with water, dried, and recrystallized from methanol; m.p. 209-211°. The substance was freely soluble in methanol, ether, and acetone, less so in benzene.

7.467 mg substance: 0.284 ml N_2 (20.5°, 723 mm). Found %: N 4.20. $C_{16}H_{19}O_5NS$. Calculated %: N 4.15.

<u>Attempt to close the β-lactam ring</u>. a) By heating the free acid. 4 grams of 2-(a-phenyl-a-carbethoxymethyl)-thiazolidine-4-carboxylic acid was heated in a round-bottomed flask on an oil bath to 100-120° for 6 hours. No changes occurred in the substance. At 150-160° the substance melted and gave off carbon dioxide (precipitate of barium carbonate with baryta water) and hydrogen sulfide.

<u>b) Heating the sodium salt</u>. 4 grams of 2-(a-Phenyl-a-carbethoxymethyl)-thiazolidine-4-carboxylic acid was dissolved in 20 ml of absolute methanol, and a 20% solution of sodium methylate in methanol was added. The methanol was driven off in vacuo to dryness. The remaining thick residue was dissolved in 25 ml of anhydrous toluene, and the latter was driven off until the distillate was completely transparent. Heating on a boiling water bath was continued for 4 hours. The toluene was driven off, and the residue heated for another 4 hours with 25 ml of absolute toluene.

After the toluene had been driven off in vacuo, the residue was dissolved in 100 ml of water, treated with charcoal, filtered, chilled, and then acidulated with hydrochloric acid until its reaction with Congo red was weakly acid. The next day the resultant crystals were filtered out, dried, and washed with ether. M.p. 168-169° (with decomposition). The mixed melting point with the initial compound exhibited no depression.

<u>2-(a-Phenyl-a-carbomethoxymethyl)-thiazolidine-4-carboxylic acid</u>. The methyl ester of formylphenylacetic acid, prepared by the method described in the literature [7], was used in a mixture of the a and β forms.

5.5 grams of l-cysteine hydrochloride, 5.7 g of methyl formylphenylacetate, and 2 ml of water were heated and vigorously stirred on a boiling water bath for 15 minutes. The reaction mass was gradually poured into 100 ml of cold water, and 25 ml of an 8% solution of sodium bicarbonate was slowly added. The next day the crystalline precipitate was filtered out, washed with water, and dried, the dry substance being washed with ether. M.p. 170-171° (with decomposition).

6.144 mg substance: 0.280 ml N_2 (21.8°, 729.6 mm). 6.737 mg substance: 0.297 ml N_2 (22.3°, 728.5 mm). Found %: N 5.07, 4.89. $C_{13}H_{15}O_4NS$. Calculated %: N 4.98.

When the free acid was heated to 160-170°, it was decarboxylated as in the case of the carbethoxy analog.

<u>Saponifying ethyl formylphenylacetate</u>. 2 grams of the ester was dissolved in 25 ml of alcohol, 24 ml of a 1N solution of sodium hydroxide was added, and the whole was allowed to stand at room temperature for 48 hours. Then 24 ml of a 1N solution of hydrochloric acid was added, and the solution was evaporated in vacuo on a water bath. Lustrous lamellar crystals with an m.p. of 76° soon settled out. Their mixed melting point with phenylacetic acid exhibited no depression.

<u>Diethyl acetal of ethyl formylphenylacetate</u>. 80 grams of ethyl formylphenylacetate was dissolved in 300 ml of absolute ethyl alcohol and 3 g of hydrogen chloride was passed through the solution, after which the solution was refluxed for 3 hours. When it had cooled, 10 g of a 50% solution of potassium hydroxide was added, the precipitated potassium chloride being filtered out 10 minutes later, the alcohol driven off in vacuo, and the residual oil dissolved in 200 ml of ether. The ether solution was washed at 0° with 120 ml of a 10% solution of potassium hydroxide and then with water and dried with sodium sulfate, after which the ether was driven off. The residue was fractionated, a fraction with a b.p. of 142-143° at 9-10 mm being collected. The yield

totaled 40 g. A colorless oil with an extremely faint odor and a sp.gr. of 1.0397 at 20°.

5.149 mg subs.: 12.875 mg CO_2; 3.578 mg H_2O. 4.600 mg subs.: 11.504 mg CO_2; 3.233 mg H_2O.
Found %: C 68.19, 68.2; H 7.76, 7.86. $C_{15}H_{22}O_4$. Calculated %: C 67.67; H 8.36.

Diethyl acetal of formylphenylacetic acid. 40 g of the diethyl acetal of ethyl formylphenylacetate, 120 ml of methanol, 20 g of a 50% solution of sodium hydroxide, and 10 ml of water were allowed to stand for two days at 15-20°. Then the methanol was driven off in vacuo on a water bath. The remaining solution was diluted with 200 ml of water and extracted 3 times with ether, the extracts being discarded.

The ether was driven out of the aqueous solution of the product, which was treated with 2 g of activated charcoal and filtered, the filtrate being carefully neutralized at 0° with hydrochloric acid until its reaction with Congo red was weakly acid. The resulting crystalline precipitate was filtered out, washed thoroughly with cold water, dried in a vacuum desiccator, and recrystallized from toluene. The yield totaled 25 g, with a m.p. of 121-123° (with decomposition). Lamellae, freely soluble in alcohol and ether, less so in benzene.

0.1033 g subs.: 4.6 ml 0.1 N NaOH. 0.0544 g subs.: 2.35 ml 0.1 N NaOH. Found %: COOH 20.04, 19.44;
OC_2H_5 38.38. $C_{13}H_{18}O_4$. Calculated %: COOH 18.91; OC_2H_5 38.38.

When the diethyl acetal of formylphenylacetic acid was heated in vacuo on an oil bath at 140-150°, a substance with a b.p. of 85-88° at 11 mm was driven off. A colorless oil with a geranium odor that exhibited a silver mirror reaction. It was identified as phenylacetaldehyde [8].

4.317 mg subs.: 12.689 mg CO_2; 2.765 mg H_2O. Found %: C 80.16; H 7.18. C_8H_8O.
Calculated %: C 80.00; H 6.71.

Oxymethylenephenylacetic acid. 9 g of the diethyl acetal of formylphenylacetic acid was mixed with 25 ml of conc.hydrochloric acid at 0° in a 50-ml round-bottomed flask for 5 hours while anhydrous hydrogen chloride was passed through the flask. The reaction mass thickened. 50 ml of cold water was added, and the precipitate was filtered out 30 minutes later and thoroughly washed with ice water. Then it was dried in a vacuum desiccator. Prisms with a m.p. of 101-103°, which had the odor of phenylacetaldehyde (geranium). The substance was washed with light petroleum ether. It was freely soluble in all the ordinary organic solvents, with the exception of gasoline.

The pungent odor of phenylacetyldehyde appeared when it was heated with water or when it was stored. It had the oxymethylene form, an aqueous solution being turned a strong blue by ferric chloride. Ammoniacal silver nitrate was hardly reduced at all by it. It decolorized a bromine solution. It was rapidly decarboxylated in pyridine, yielding phenylacetaldehyde.

4.504 mg subs.: 11.019 mg CO_2; 1.846 mg H_2O. 4.173 mg subs.: 10.210 mg CO_2; 1.772 mg H_2O.
Found %: C 66.72, 66.73; H 4.59, 4.75. C_9H_8O. Calculated %: C 65.85; H 4.87.

2-Benzylthiazolidine-4-carboxylic acid. 0.9 g of l-cysteine hydrochloride, 1 g of oxymethylenephenylacetic acid, and 4 ml of methanol were mixed together, and the resulting solution was allowed to stand at room temperature. Carbon dioxide began to be given off within a few minutes. Two days later the mass was gradually poured into 20 ml of water, carefully neutralized with 5 ml of an 8% solution of sodium bicarbonate until its reaction with Congo red was weakly acid, and then diluted 1:1 with acetone. The resultant crystalline precipitate was filtered out, washed with water and dried in a vacuum desiccator. A small amount of the substance was quickly recrystallized from hot water. Thin, elongated needles with a m.p. of 154-165° (with decomposition). Sparingly soluble in water, more so in ether and alcohol, insoluble in gasoline.

5.950 mg subs.: 0.285 ml N_2 (19°, 738 mm). 0.5743 g subs.: 0.0758 g H_2O. Found %: N 5.43; H_2O 13.2.
$C_{11}H_{13}O_2NS \cdot 2H_2O$. Calculated %: N 5.4; H_2O 13.89.

The same substance was secured by condensing 1 g of cysteine hydrochloride at 50° for 8 hours with 0.9 g of phenylacetaldehyde in 1 ml of water and 5 ml of methanol, as well as by condensing the cysteine hydrochloride with oxymethylenephenylacetic acid in pyridine.

2-(α-Phenyl-α-carboxymethyl)-thiazolidine-4-carboxylic acid.[*] 2 g of l-cysteine hydrochloride was heated with 0.8 ml of water and 3 g of the diethyl acetal of formylphenylacetic acid were heated and stirred together for 5 minutes on a boiling water bath. At first the mass foamed a little, but then boiled up, giving off alcohol vapor, and became homogeneous. It crystallized quickly upon cooling. The crystalline mass was treated with 50 ml of

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[*] This synthesis could not be repeated.

acetone, the crystals being filtered out and washed with acetone. The substance was recrystallized from 90% of acetone. Short little needles with a m.p. of 169-170° (with decomposition). Freely soluble in hot water, soluble in methanol, and insoluble in acetone, benzene, and chloroform. When boiled in water. it decomposed into cysteine, phenylacetaldehyde. and carbon dioxide.

10.072 mg subs.: 3.86 mg 0.01 N H_2SO_4. 0.0804 g subs.: 6.0 ml 0.1 N NaOH. 0.0688 g subs.: 5.15 ml 0.1 N NaOH. Found %: N 5.37; COOH 33.57, 33.68. $C_{12}H_{13}O_4NS$. Calculated %: N 5.24; COOH 33.69.

S-β-(α-Phenyl-α-carboxy)-ethylenecysteine. 3 g of the diethyl acetal of formylphenylacetic acid was stirred at 0° for 3 hours with 20 ml of concentrated hydrochloric acid. 2 g of dl-cysteine hydrochloride was added to the reaction mass, and stirring was continued for 3 more hours at from 0° to 5°, the oxymethylenephenylacetic acid dissolving. The reaction with sodium nitroprusside for a free mercapto group was negative. The solution was then evaporated in vacuo to dryness. A crystalline deposit was left on the wall of the flask, which was dissolved in 15 ml of water; the solution was neutralized until its reaction with Congo red was barely acid, a very thick oil that gradually crystallized settling out. The substance was recrystallized from hot water. Needles with a m.p. of 164-165° (with decomposition).

This same compound was precipitated by adding sodium carbonate to a solution of its hydrochloride. It was freely soluble in hydrochloric acid, sparingly soluble in water and methanol, and insoluble in chloroform, acetone, toluene, ethyl acetate, and gasoline.

7.304 mg subs.: 0.304 ml N_2 (23.5°, 747 mm). 11.309 mg subs.: 4.04 ml 0.01 N H_2SO_4. 11.434 mg subs.: 3.93 ml 0.01 N H_2SO_4. 0.1266 g subs.: 0.1108 g $BaSO_4$. Found %: N 4.87, 5.00, 4.81; S 12.01. $C_{12}H_{13}O_4NS$. Calculated %: N 5.24; S 11.98.

0.4 g of the substance was dissolved in 20 ml of water containing 4 ml of an 8% solution of sodium bicarbonate. The solution was heated to 70° for 1.5 hours, after which it was treated with charcoal, filtered, and acidulated at 0° with 10% H_2SO_4 until its reaction with Congo red was weakly acid. A crystalline precipitate (clusters) gradually settled out. The next day the substance was filtered out and purified by converting it into a sodium salt. Its mixed melting point with S-β-(α-phenyl-α-carboxy)-ethylenecysteine exhibited no depression.

Ethylmethoxymethylenephenylacetate. 13 g of ethyl oxymethylenephenylacetate was added to 60 ml of a 5% solution of sodium hydroxide chilled to 0°; the whole was agitated vigorously and then the undissolved substance was extracted 2 or 3 times with ether, which was discarded. 7 g of dimethyl sulfate was added to the aqueous solution, and the reaction mass was thoroughly stirred for 12 hours at 15-20°. The supernatant oil was extracted with ether. The ether extract was washed with a solution of sodium bicarbonate and dried with sodium sulfate, the ether was driven off, and the remaining oil was distilled in vacuo, a fraction with a b.p. of 124-125° at 3 mm being collected. The yield was 6.8 g.

S-β-(α-Phenyl-α-carbethoxy)-ethylene-dl-cysteine hydrochloride. 6.5 g of ethyl methoxymethylenephenylacetate was stirred at 0° with 5 g of dl-cysteine hydrochloride and 10 ml of conc. hydrochloric acid, and hydrogen chloride was passed through the reaction mass for 1 hour, after which stirring was continued for another 2 hours. A white crystalline substance settled out after some time had passed. The mass was diluted with an equal quantity of water, and the crystals were filtered out, washed thoroughly with 20% hydrochloric acid, and dried in a vacuum desiccator over alkali and sulfuric acid. The substance was dissolved in acetone, and the solution was treated with ether, a white crystalline precipitate weighing 6.2 g with a m.p. of 169-172° (with decomposition) settling out.

The substance was freely soluble in water and methanol, somewhat less in acetone, and only very slightly soluble in ether and toluene. The substance was precipitated from aqueous solutions when conc. hydrochloric acid was added. Its nitroprusside reaction for a mercapto group was negative, and it could not be titrated with iodine.

7.359 mg subs.: 2.16 ml 0.01 N H_2SO_4. 9.631 mg subs.: 2.86 ml 0.01 N H_2SO_4. Found %: N 4.11, 4.16; S 9.7; Cl 10.65, 10.81. $C_{14}H_{18}O_4NSCl$. Calculated %: N 4.22; S 9.65; Cl 10.71.

S-β-(α-Phenyl-α-carbethoxy)-ethylene-dl-cysteine. 2 g of S-β-(α-phenyl-α-carbethoxy)-ethylene-dl-cysteine hydrochloride was dissolved in 10 ml of methanol, and 0.7 ml of pyridine was added. The next day the precipitated crystals were filtered out and washed with methanol and ether. Thin lamellae with a m.p. of 153-154° (with decomposition). The substance was sparingly soluble in cold water and more soluble in hot, sparingly soluble in methanol and ethyl alcohol. and insoluble in acetone, benzene, and gasoline; it was soluble in dilute alkalies and mineral acids. Its ninhydrin reaction for an α-amino acid was positive. It contained no mercapto group, nor was it titrated by iodine. When it was dissolved in a 5% sodium hydroxide solution, a nitroprusside reaction

indicated the presence of a mercapto group. It formed no precipitate when reacted with mercurous chloride in an alcoholic solution.

11.466 mg subs.: 3.88 ml 0.01 N H_2SO_4. Found %: N 4.74. $C_{14}H_{17}O_4NS$. Calculated %: N 4.74.

0.6 g of the substance was dissolved by heating it in 10 ml of a 2% solution of sodium bicarbonate. The solution was heated to 70° on a water bath for 1.5 hours. Then the solution was chilled to 0° and acidulated with 2% hydrochloric acid. The resultant flocculent precipitate was filtered out, washed with water, dried, and recrystallized from methanol. Needles with a m.p. of 169-170° (with decomposition). Their mixed melting point with 2-(a-phenyl-a-carbethoxymethyl)-thiazolidine-4-carboxylic acid exhibited no depression.

The thiazolidine compound was also produced by treating S-β-(a-phenyl-a-carbethoxy)-ethylene-dl-cysteine with aqueous ammonia.

S-β-(a-Phenyl-a-carbethoxy)-ethylene-N-acetylcysteine. 1 g of S-β-(a-phenyl-a-carbethoxy)-ethylenecysteine was gradually added to 3 ml of anhydrous pyridine that contained 0.5 g of acetic anhydride. The substance dissolved after it had been stirred for 1 hour. Then the solution was gradually added to 12 ml of 20% sulfuric acid at 0°. The thick yellow oil that separated out was extracted with ether. The ether extract was washed with 10 ml of water and then agitated violently for 5 minutes with 10 ml of a 4% sodium bicarbonate solution. The aqueous solution was separated chilled to 0°, and acidulated with 3 ml of 10% sulfuric acid, the white emulsion that resulted being extracted with ether. The ether solution was washed with water and dried over sodium sulfate, and the ether was driven off in vacuo. This left a pale-yellow mass with a m.p. of 48-52°. It was very freely soluble in methanol butyl alcohol, ether, ethyl acetate, acetone, and chloroform, sparingly soluble in toluene, and insoluble in petroleum ether and dilute sulfuric acid.

8.582 mg subs.: 2.6 ml 0.01 N H_2SO_4. 0.0505 g subs.: 1.5 ml 0.1 N NaOH (in methyl alcohol). Found %: N 4.24; COOH 13.36. $C_{16}H_{19}O_5NS$. Calculated %: N 4.15; COOH 13.3.

S-β-(a-phenyl-a-carbomethoxy)-ethylenecysteine hydrochloride. We used methyl formylphenylacetate instead of methyl methoxymethylenephenylacetate in synthesizing the above compound. The yield was lower, since only the oxymethylene form reacts with cysteine hydrochloride, yielding an S-substitution derivative of cysteine. 2.5 g of cysteine hydrochloride was stirred with 2.8 g of methyl formylphenylacetate and 10 ml of conc. hydrochloric acid for 6 hours at 0°. A precipitate began to settle out toward the end of the reaction. The next day the precipitate was filtered out, washed three times with hydrochloric acid, dried in a vacuum desiccator, dissolved in acetone, and precipitated with ether. The substance was recrystallized from hydrochloric acid, dried, and washed with acetone and ether. M.p. 169-172° (with decomposition). Its physical and chemical properties were the same as those of its carbethoxy analog mentioned above. The yield was 1.2 g.

0.1869 g subs.: 0.1318 g $BaSO_4$. Found %: S 9.68. $C_{13}H_{16}O_4NSCl$. Calculated %: S 10.07.

S-β-(a-Phenyl-a-carbomethoxy)-ethylenecysteine. 4.2 g of the hydrochloride was dissolved in 21 ml of methanol, and 2.1 g of pyridine was added. The next day the crystalline precipitate was filtered out and washed with methanol and ether. The yield totaled 2.55 g with a m.p. of 151-153° (with decomposition). Its properties resembled those of S-β-(a-phenyl-a-carbethoxy)-ethylenecysteine.

7.393 mg subs.: 0.332 ml N_2 (20.5°, 743 mm). Found %: N 5.11. $C_{13}H_{15}O_4NS$. Calculated %: N 4.98.

0.3 g of S-β-(a-phenyl-a-carbomethoxy)-ethylene cysteine was mixed with 3 ml of anhydrous pyridine and 0.15 g of triethylamine and set aside to stand for 3 days, the precipitate gradually dissolving. The solution was poured into 12 ml of a 25% solution of sulfuric acid, the resulting white precipitate being dissolved in 20 ml of ether. The ether solution was discarded. A substance with a m.p. of 172-173° (with decomposition) crystallized gradually from the aqueous solution. Its mixed melting point with 2-(a-phenyl-a-carbomethoxymethyl)-thiazolidine-4-carboxylic acid exhibited no depression.

2-(a-Phenyl-a-carbomethoxymethyl)-N-acetylthiazolidine-4-carboxylic acid. 2 g of 2-(a-phenyl-a-carbomethoxymethyl)-thiazolidine-4-carboxylic acid was mixed with 5 g of absolute anhydrous pyridine, and 1.5 ml of acetic anhydride was added. The next day the reaction mass was gradually added to 40 ml of 10% sulfuric acid chilled to 0°. The white precipitate was filtered out, washed with water dissolved in a dilute aqueous solution of ammonia, and treated with charcoal, the resultant solution being poured into 30 ml of 10% sulfuric acid at 0°. The precipitate was filtered out, washed with water, dried, and recrystallized from a small quantity of methanol. Thin, elongated needles with a m.p. of 222-223° (with decomposition).

6.505 mg subs.: 0.249 ml N_2 (16°, 724 mm). Found %: N 4.34. $C_{15}H_{17}O_5NS$. Calculated %: N 4.34.

2-(α-Phenyl-α-carboxymethyl)-N-acetylthiazolidine-4-carboxylic acid. 1.5 g of the substance was dissolved in 10 ml of a 10% solution of sodium hydroxide and set aside for 2 days at room temperature. The solution was chilled to 0° and acidulated with 10% sulfuric acid. The oil that separated was extracted with 250 ml of ether. The ether solution was washed with a small quantity of water and dried with anhydrous sodium sulfate, after which the ether was driven off to a total volume of 10 ml. The resultant white crystalline precipitate weighed 0.6 g. Needles with a m.p. of 206-207° (with swelling). Freely soluble in water and methanol, less so in ether.

5.024 mg 0.207 ml N_2 (18°, 748.5 mm). Found%: N 4.76. $C_{14}H_{15}O_5NS$. Calculated %: N 4.53.

SUMMARY

1. Condensing dl-cysteine with ethyl formylphenylacetate yielded 2-(α-phenyl-α-carbethoxymethyl)-thiazolidine-4-carboxylic acid, from which no compound containing a thiazolidine-β-lactam ring system could be obtained.

2. Oxymethylenephenylacetic acid has been obtained from the diethyl acetal of ethyl formulphenylacetate. Condensing this acid with l-cysteine yielded 2-benzylthiazolidine-4-carboxylic acid.

3. When dl-cysteine was reacted with oxymethylenephenylacetic acid in concentrated hydrochloric acid, S-β-(α-phenyl-α-carboxy)-ethylenecysteine was produced.

4. Reacting dl-cysteine with ethyl methoxymethylenephenylacetate in concentrated hydrochloric acid yielded S-β(α-phenyl-α-carbethoxy)-ethylenecysteine, which could be readily converted into 2-(α-phenyl-α-carbethoxymethyl)-thiazolidine-4-carboxylic acid.

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THE NITRATION OF ac-1-TETRAHYDRONAPHTHOIC ACID

## AND THE TRANSFORMATIONS OF NITRO-ac-1-TETRAHYDRONAPHTHOIC ACIDS

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Our researches on the carboxylic and thiocarboxylic acids of tetrahydronaphthalene [1] up to now have dealt principally with compounds having substituents in the aromatic part of the ring: we thought it would be interesting to make a study of acids that had functional groups in both parts of the tetrahydronaphthalene molecule (both the hydrogenated and the nonhydrogenated). The initial substance used for synthesizing these compounds in the present research was ac-1-tetrahydronaphthoic acid, which was nitrated. The nitration of this acid, which had been not been previously investigated, interested us not only as a means of securing compounds of the specified type, but also as providing the opportunity of pursuing our study of the group orientation phenomena in the tetralin ring.

Nitration of ac-1-tetrahydronaphthoic acid with nitric acid (sp.gr. 1.5) produced a dinitro acid, the yield being 90%, while when the sp.gr. of the nitric acid used was 1.4, we secured a mixture of mononitro acids, with a yield of 70%. The method we have developed was employed to separate this mixture into two mononitro acids, one with a m.p. of 143° and the other with a m.p. of 163°. Renitration of each of these mononitro acids produced the same dinitro acid, identical with the dinitro acid secured when the ac-1-tetrahydronaphthoic acid was directly nitrated with fuming nitric acid.

We determined the positions at which the nitro groups entered by employing the transformations of the nitro acids that either led directly to substances of known structure or established a genetic relationship between the latter and the initial nitro compounds. One of these transformations is the following: oxidizing the dinitro tetrahydronaphthoic acid, which yielded 3,5-dinitrophthalic acid, evidence of the meta position of the nitro groups to each other in the initial dinitro-1-tetrahydronaphthoic acid; hence, one of the formulas given below (I and II) may be assigned to the latter:

The nitro groups in the mononitro acids were reduced catalytically, the nitro acid with a m.p. of 143° yielding amino-1-tetrahydronaphthoic acid with a m.p. of 200.5-201.5°, and the nitro acid with a m.p. of 163° yielding an amino acid with a m.p. of 170-171°.
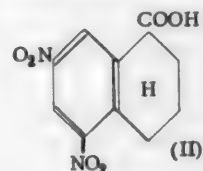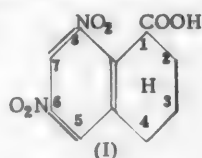
Of the amino-ac-1-tetrahydronaphthoic acids, only one has been described in the literature so far—8-amino-ac-1-tetrahydronaphthoic acid [2]. The physicochemical properties of this amino acid and of its derivatives were not the same as the constants of the amino acids we had synthesized or their derivatives; therefore, the nitro and amino groups could not occupy the 8 position in our compounds, which determined the composition of the dinitro acid first of all: it could be nothing but 5,7-dinitro-(1,2,3,4)-tetrahydro-1-naphthoic acid. Since this same dinitro acid was produced by renitrating each of the two isomeric mononitro acids, one of the latter had to be 5-nitro-(1,2,3,4)-tetrahydro-1-naphthoic acid, and the other 7-nitro-(1,2,3,4)-1-tetrahydronaphthoic acid, though we did not know which was which. To ascertain the structure of the mononitro acids we synthesized the 5-amino-1-naphthoic acid described in the literature [3] and reduced it with sodium and isoamyl alcohol. Since in this method of reduction the amino and carboxyl groups at the α-positions in naphthalene orient the hydrogen to the part of the ring where the carboxyl group is located, we might expect 5-amino-(1,2,3,4)-tetrahydro-1-naphthoic acid, identical with one of our amino acids, to be formed. As a matter of fact, the reaction resulted in formation of an amino acid with a m.p. of 200-201°, which was identical with the amino acid we had synthesized by reducing the mononitro acid with a m.p. of 143°; it followed that the latter and its respective amino acid were 5-nitro-(amino)-1,2,3,4-tetrahydro-1-naphthoic acids.

The sum total of all these findings also indicated that the second mononitro acid, with a m.p. of 163°, and its corresponding amino acid were nothing else than 7-nitro-(amino)-tetrahydro-1-naphthoic acids. The β-position of the amino group in the 7-amino-1-tetrahydronaphthoic acid was likewise confirmed by the fact that its decarboxylation yielded the well-known ar-β-tetrahydronaphthylamine.

In addition to the conversions required to determine the structure of the compounds we had synthesized, we also carried out a few others: the 5,7-dinitro-1-tetrahydronaphthoic acid was reduced to 5,7-diamino-1-tetrahydronaphthoic acid, decarboxylation of which yielding the corresponding diamine; and we synthesized the 5(7)-nitro-1-tetrahydrothionaphthoic acids and the simplest derivatives of all the nitro and amino acids referred to above.

5-Nitro-ac-tetrahydro-1-naphthoic acid and 7-nitro-ac-tetrahydro-1-naphthoic acid. 60 g of ac-tetra-hydro-1-naphthoic acid was added in one batch to 350 ml of HNO_3 (sp.gr. 1.40). The mixture was heated gently to set off the reaction. The temperature within the reaction mixture was maintained at 40-41°. The ac-tetrahydro-1-naphthoic acid dissolved gradually, a crystalline precipitate of the nitro compounds beginning to settle out after some time. 1.5 hours later the reaction mixture was cooled to room temperature.

The precipitate was suction-filtered and washed, first with nitric acid, sp.gr. 1.40, and then with water. This yielded 39 g of a slightly yellowish crystalline substance with a m.p. of 115-122°. The acid mother liquor was highly diluted with water. A tarry mass settled out, which solidified after some time had elapsed. The resultant yellow substance was filtered out and recrystallized from toluene. This yielded 10 g of a substance with a m.p. of 115-122°. Neutralization of the diluted nitric acid solution with soda yielded another 3 g of a substance with a lower melting point. When 60 g of ac-tetrahydro-1-naphthoic acid was nitrated, for example, we secured 52 g of a mixture of isomeric nitro acids. The yield was 69% of the theoretical.

The mixture of nitro acids produced by nitration dissolved readily in a 10% soda solution. When the alkaline solutions were fractionally acidulated with dilute hydrochloric acid, the first nitro acid to settle out was the one with the higher melting point — 7-nitro-(1,2,3,4)-1-tetrahydronaphthoic acid. Its m.p. was 163° after recrystallization from toluene. As acidulation was continued, 5-nitro-(1,2,3,4)-1-tetrahydronaphthoic acid settled out, its melting point being 143° after recrystallization from toluene [*], while the last precipitate was a mixture of the same isomers, with a m.p. of 110-130°, which could not be separated by this method.

Separating isomeric nitrotetrahydronaphthoic acids via their ethyl esters. 52 g of a mixture of isomeric 5- and 7-nitro-ac-tetrahydro-1-naphthoic acids, with a m.p. of 115-122°, was heated for 8 hours with 500 ml of absolute ethyl alcohol and 15 ml of concentrated sulfuric acid. When the reaction was over, the bulk of the alcohol was driven off, a small quantity of water was added to the residue, and the resultant oil was extracted with ether. The ether solution was washed with a soda solution and then with water. The aqueous alkaline solution was acidified. This yielded 1 g of a mixture of nitro acids that had not entered into the esterification reaction. The ether solution was dried over anhydrous Na_2SO_4, after which the ether was driven off as completely as possible. A small quantity of petroleum ether was added to the residue and the mixture was chilled with ice. The resulting precipitate was filtered out. This yielded 16 g of a slightly yellowish crystalline substance with a m.p. of 77-78° constituting the ethyl ester of 7-nitro-ac-tetrahydro-1-naphthoic acid. The ethyl ester with a m.p. of 77-78° was saponified by heating it with 40% acetic acid and a small amount of hydrochloric acid. Upon cooling, 7-nitro-ac-tetrahydro-1-naphthoic acid crystallized out; its m.p. was 163° after recrystallization from toluene.

7-Nitro-ac-tetrahydro-1-naphthoic acid consisted of nearly colorless crystals, which were freely soluble in alcohol and hot toluene, and slightly soluble in cold toluene and carbon tetrachloride.

6.629 mg subs.: 0.366 ml N_2 (20.5°, 733.0 mm). 6.648 mg subs.: 0.372 ml N_2 (23.0°, 740.0 mm). 3.877 mg subs.: 8.522 mg CO_2; 1.771 mg H_2O. Found %: C 59.94; H 5.11; N 6.19, 6.28. $C_{11}H_{11}O_4N$. Calculated %: C 59.74; H 4.97; N 6.34.

The petroleum ether mother liquor, which contained the ethyl ester of 5-nitro-ac-tetrahydro-1-naphthoic acid with a trace of the ethyl ester of the 7-nitro acid, was evaporated until the solvent had been driven off. The liquid residue was saponified by heating it with dilute acetic acid (40%) containing a small percentage of hydrochloric acid. The customary treatment yielded a mixture of nitro acids with a m.p. of 120-133°. The mixture of nitro acids was dissolved in a 10% soda solution, and dilute hydrochloric acid was gradually added to the resultant solution. At first 5-nitro-ac-tetrahydro-1-naphthoic acid settled out, its m.p. being 143° after recrystallization from toluene. The amount of the 5-nitro acid secured was about half the mixture initially used. As acidification continued, a mixture of nitro acids with a m.p. of 123-133° settled out. This mixture was re-esterified, the entire process of precipitating and separating the isomeric esters and acids described above being repeated.

Double esterification and saponification of 52 g of the mixture yielded 14 g of 7-nitro-ac-tetrahydro-1-naphthoic acid and 17 g of 5-nitro-ac-tetrahydro-1-naphthoic acid. 5-Nitro-ac-tetrahydro-1-naphthoic acid consisted of crystals with a greenish tinge, m.p. 143°, freely soluble in acetone, ether, alcohol, and hot toluene, and sparingly soluble in cold toluene.

8.380 mg subs.: 0.477 ml N_2 (25.5°, 732.0 mm). 3.071 mg subs.: 6.747 mg CO_2; 1.369 mg H_2O. Found %: C 59.92; H 4.99; N 6.27. $C_{11}H_{11}O_4N$. Calculated %: C 59.74; H 4.97; N 6.34.

[*] Separating the nitro acids by this method led us to assume that their acidities differed; further research (see the following experiment) and potentiometric titration, however, indicated that their acidities were identical. The sequence in which the isomers were precipitated from aqueous alkaline solutions depended, apparently, upon quantitative relationships.

Ethyl ester of 5-nitro-ac-tetrahydro-1-naphthoic acid.   4.5 g of 5-nitro-ac-tetrahydro-1-naphthoic acid was heated to boiling for 8 hours with 40 ml of absolute ethyl alcohol and 3 drops of conc. sulfuric acid. When the reaction was over, the alcohol was driven off, and the residue extracted with ether. The ether solution was washed with a soda solution and with water and then dried with anhydrous sodium sulfate. The ether was driven off, and the residue (4 g) distilled in vacuo.

The ethyl ester of 5-nitro-ac-tetrahydro-1-naphthoic acid, was a greenish oil, with a b.p. of 171° at 1.5-2 mm; d_4^{20} 1.2140, n_D^{20} 1.5428.

5.223 mg subs.: 0.275 ml N_2 (30.0°, 724.0 mm). Found %: N 5.64. $C_{13}H_{15}O_4N$. Calculated %: N 5.62.

5-Nitro-ac-tetrahydro-1-naphthoyl chloride. 3.0 g of 5-nitro-ac-tetrahydro-1-naphthoic acid, with a m.p. of 143°, was heated to boiling with 9 ml of thionyl chloride for 3 hours. When the reaction was over, the excess thionyl chloride was driven off. The last traces of the thionyl chloride were eliminated by adding some absolute benzene, which was then likewise driven off in vacuo. A small quantity of petroleum ether was added to the residual mass, and the mixture was strongly chilled with ice and salt. Vigorous rubbing with a glass rod threw down a crystalline precipitate, which was filtered out and recrystallized from ligroin.

5-Nitro-ac-tetrahydro-1-naphthoyl chloride consisted of colorless needles with a m.p. of 53-54°, which were readily soluble in benzene and acetone, though only slightly soluble in ligroin and petroleum ether.

0.1457 g subs.: 0.0864 g AgCl. Found %: Cl 14.67. $C_{11}H_{10}O_3NCl$. Calculated %: Cl 14.82.

Diethylaminoethyl ester of 5-nitro-ac-tetrahydro-1-naphthoic acid (hydrochloride). 1.17 g of diethylamino-ethanol was added to a solution of 3 g of 5-nitro-ac-tetrahydro-1-naphthoyl chloride in 50 ml of absolute benzene, and the mixture was heated to boiling for 3 hours. The hydrochloride that settled out upon cooling was dissolved in 2-3 ml of absolute ethyl alcohol, and absolute ether was added to the alcoholic solution until precipitation was complete. This yielded 3.4 g with a m.p. of 120-122°. Reprecipitation from alcohol by ether yielded the hydrochloride of the diethylaminoethyl ester of 5-nitro-ac-tetrahydro-1-naphthoic acid as a colorless, nonhygroscopic substance with a m.p. of 125-127°, which was readily soluble in water and alcohol, and sparingly so in benzene and chloroform.

8.115 mg subs.: 0.547 ml N_2 (21.5°, 740.0 mm).   7.140 mg subs.: 0.490 ml N_2 (21.5°, 738.0 mm). Found %: 7.62, 7.73. $C_{17}H_{24}O_4N_2 \cdot HCl$. Calculated %: N 7.85.

Ethyl ester of 7-nitro-ac-tetrahydro-1-naphthoic acid. 1 g of 7-nitro-ac-tetrahydro-1-naphthoic acid was heated to boiling for 8 hours with 10 ml of absolute ethyl alcohol and 3 drops of conc. sulfuric acid. The usual processing yielded the ethyl ester of 7-nitro-ac-tetrahydro-1-naphthoic acid as colorless, silky, elongated needles with a m.p. of 77-78°. Readily soluble in ether, alcohol, and chloroform, soluble when heated in petroleum ether, and rather slightly soluble in petroleum ether in the cold.

8.211 mg subs.: 0.418 ml N_2 (29.5°, 730.5 mm). Found %: N 5.52. $C_{13}H_{15}O_4N$. Calculated %: N 5.62.

7-Nitro-ac-tetrahydro-1-naphthoyl chloride. 3.0 g of 7-nitro-ac-tetrahydro-1-naphthoic acid was heated to boiling for 3 hours with 9 ml of thionyl chloride. The subsequent processing was like that described for the 5-nitro isomer.

When recrystallized from ligroin, the 7-nitro-ac-tetrahydro-1-naphthoyl chloride consisted of colorless needles with a m.p. of 97-98°, which were freely soluble in benzene and, when heated, in ligroin, and sparingly soluble in cold ligroin and in petroleum ether.

0.1287 g subs.: 0.0759 g AgCl. 0.1582 g subs.: 0.0937 g AgCl. Found %; Cl 14.57, 14.65. $C_{11}H_{10}O_3NCl$. Calculated %: Cl 14.82.

Diethylaminoethyl ester of 7-nitro-ac-tetrahydro-1-naphthoic acid (hydrochloride). The reaction conditions were the same as those employed in the synthesis of the alkamino ester of 5-nitro-ac-tetrahydro-1-naphthoic acid.

3.0 g of 7-nitro-ac-tetrahydro-1-naphthoyl chloride and 1.17 g of diethylaminoethanol yielded 3.4 g of the hydrochloride of the diethylaminoethyl ester of 7-nitro-ac-tetrahydro-1-naphthoic acid: a colorless, crystalline substance with a m.p. of 134-136°. freely soluble in water and alcohol, sparingly soluble in benzene and chloroform, and insoluble in ether.

7.730 mg subs.: 0.549 ml N_2 (21.5°, 740.0 mm). 6.270 mg subs.: 0.447 ml N_2 (22.5°, 738.0 mm). Found %: N 8.01, 7.89. $C_{17}H_{24}O_4N_2 \cdot HCl$. Calculated %: N 7.85.

5-Amino-ac-tetrahydro-1-naphthoic acid and its derivatives. a) 2.21 grams of 5-nitro-ac-tetrahydro-1-naph-thoic acid was dissolved in 100 ml of methanol. 5 g of Raney's nickel catalyst was added to the solution, and the mixture was agitated in a hydrogen atmosphere until the requisite amount of hydrogen (670 ml) had been absorbed. Reduction was carried out either at room temperature or with gentle heating to 25°. After the hydrogen had been absorbed, the catalyst was filtered out, and the alcohol was driven off in vacuo. The amino acid was recrystallized from alcohol. This yielded 1.55 g of a substance with a m.p. of 200.5-201.5° (with decomposition).

5-Amino-ac-tetrahydro-1-naphthoic acid was a colorless substance that was slightly soluble in methanol and ethyl alcohol, even less soluble in acetone and chloroform and wholly insoluble in ether.

8.437 mg substance: 0.546 ml N_2 (25.0°, 742.0 mm). Found %: N 7.24. $C_{11}H_{13}O_2N$. Calculated %: N 7.33.

5-Acetamino-ac-tetrahydro-1-naphthoic acid was synthesized by heating 5-amino-ac-tetrahydro-1-naphthoic acid with acetic anhydride in ethyl acetate for 3 hours. After the reaction was over, the precipitated acetyl deriva-tive was filtered out and recrystallized from aqueous alcohol.

5-Acetamino-ac-tetrahydro-1-naphthoic acid was a colorless crystalline substance with an m.p. of 232-232.5° (with decomposition), which was insoluble in ethyl acetate and soluble in methanol and ethyl alcohol.

7.947 mg substance: 0.422 ml N_2 (22.0°, 736.0 mm). Found %: N 5.95. $C_{13}H_{15}O_3N$. Calculated %: N 6.01.

b) The 5-Amino-1-naphthoic acid [1] was dissolved in 250 ml of hot absolute isoamyl alcohol, and 15 ml of metallic sodium was added to the hot solution (boiling of the isoamyl alcohol being continued throughout the reaction). After all the sodium had dissolved, the isoamyl alcohol was driven off with steam.

The remaining aqueous-alkaline solution was neutralized with acid (using litmus paper) and then filtered. The filtrate was evaporated in vacuum and cooled, a crystalline mass of sodium acetate being thrown down. The minimum quantity of water was added to dissolve the latter. The insoluble brown precipitate was filtered out. This yielded 2.3 g of a substance with an m.p. of 180-190°.

Double recrystallization from alcohol raised the m.p. of the substance to 200-201° (with decomposition); it proved to be 5-amino-ac-tetrahydro-1-naphthoic acid. Its mixed melting point with the 5-amino-ac-tetrahydro-1-naphthoic acid we had synthesized by another method was 200.5-201.5° (with decomposition).

8.793 mg substance: 0.574 ml N_2 (24.0°, 743.0 mm). 8.578 mg substance: 0.549 ml N_2 (24.0°, 743.0 mm). Found %: N 7.33, 7.19. $C_{11}H_{13}O_2N$. Calculated %: N 7.33.

0.2 g of the 5-amino-ac-tetrahydro-1-naphthoic acid prepared in this experiment was heated to 80° for 3 hours with 0.5 ml of acetic anhydride and 1 ml of ethyl acetate. The precipitated acetyl derivative was filtered out and washed with ethyl acetate, m.p. 227-229°. Recrystallization from aqueous alcohol raised the m.p. of the substance to 230-231° (with decomposition). Its mixed melting point with the 5-acetamino-ac-tetrahydro-1-naphthoic acid we had synthesized earlier was 232° (with decomposition).

6.570 mg substance: 0.363 ml N_2 (21.5°, 734.5 mm). 3.607 mg substance: 8.858 mg CO_2; 2.052 mg H_2O. Found %: C 66.97; H 6.36; N 6.19. $C_{13}H_{15}O_3N$. Calculated %: C 66.96; H 6.44; N 6.01.

Ethyl ester of 5-amino-ac-tetrahydro-1-naphthoic acid. 1.3 g of 5-amino-ac-tetrahydro-1-naphthoic acid was heated to boiling for 6 hours with 30 ml of absolute ethyl alcohol and 0.6 ml of concentrated sulfuric acid. The alcohol was driven off, and the residue was treated with 10% soda solution and then extracted with ether. The ether extract was washed with soda and then with water and dried over anhydrous sodium sulfate. Driving off the ether left behind 1 g of a yellowish mass, which was distilled in vacuo.

The ethyl ester of 5-amino-ac-tetrahydro-1-naphthoic acid was a highly viscous oil, colorless and odorless, with a b.p. of 160° at 3 mm; $n_D^{19.5}$ 1.5604.

6.845 mg substance: 0.380 ml N_2 (22.0°, 747.0 mm). 17.50 mg substance: 0.954 ml N_2 (19.0° 745.0 mm). Found %: N 6.31, 6.25. $C_{13}H_{17}O_2N$. Calculated %: N 6.39.

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[1] Ekstrand [3] had previously synthesized 5-amino-1-naphthoic acid by reducing 5-nitro-1-naphthoic acid with $FeSO_4$ in ammonia. We also synthesized 5-amino-1-naphthoic acid from 5-nitro-1-naphthoic acid, but by a cata-lytic method. We used 6.5 g of 5-nitro-1-naphthoic acid, 300 ml of ethyl alcohol, and 20 g of Ni catalyst (Raney's) in the reaction. Hydrogenation was performed at 30-40°. Absorption of the requisite quantity of hydrogen and the customary processing yielded a yellowish substance with an m.p. of approximately 200°, which was impure 5-amino-1-naphthoic acid. The substance was not further refined.

Diethylaminoethyl ester of 5-amino-ac-tetrahydro-1-naphthoic acid (hydrochloride). 6 grams of Raney's nickel catalyst was added to a solution of 1.4 g of the hydrochloride of the diethylaminoethyl ester of 5-nitro-ac-tetrahydro-1-naphthoic acid in 20 ml of absolute ethyl alcohol, and the mixture was agitated in a hydrogen atmosphere. When the reaction was over, the catalyst was filtered out, and the alcohol was driven off in vacuum. 3-4 ml of absolute alcohol and 80 ml of absolute ether were added to the residue.

Rubbing with a glass rod yielded 0.75 g of a colorless crystalline substance with an m.p. of 131-132°. The hydrochloride of the diethylaminoethyl ester of 5-amino-ac-tetrahydro-1-naphthoic acid was nonhygroscopic, soluble in water, alcohol, acetone, and chloroform, and insoluble in toluene, ethyl acetate, and CCl_4.

7.685 mg substance: 0.569 ml N_2 (21.5°, 737.0 mm). 6.040 mg substance: 0.454 ml N_2 (21.0°, 745.0 mm). Found %: N 8.32, 8.56. $C_{17}H_{26}O_2N_2 \cdot HCl$. Calculated %: N 8.58.

7-Amino-ac-tetrahydro-1-naphthoic acid. 6.63 grams of 7-nitro-ac-tetrahydro-1-naphthoic acid was dissolved in 150 ml of methanol, and the solution was agitated in a hydrogen atmosphere together with 5 g of Raney's nickel catalyst. The reaction was carried out at 20-25°. After the requisite quantity of hydrogen (2000 ml) had been absorbed, the catalyst was filtered out, and the methanol was driven off in vacuo, the residue being 5.7 g of a colorless crystalline substance with an m.p. of 169-170°. Recrystallization from alcohol raised the m.p. of the 7-amino-ac-tetrahydro-1-naphthoic acid to 170-171°; it was slightly soluble in methanol, ethyl alcohol, and acetone, and insoluble in ether.

6.105 mg substance: 0.386 ml N_2 (21.5°, 738.5 mm). Found %: N 7.12. $C_{11}H_{13}O_2N$. Calculated %: N 7.33.

7-Acetamino-ac-tetrahydro-1-naphthoic acid. 0.5 gram of 7-amino-ac-tetrahydro-1-naphthoic acid was heated to 80° for 3 hours with 0.8 ml of acetic anhydride. 1 ml of glacial acetic acid was added, and when the mixture had cooled, the precipitated acetyl derivative was filtered out.

7-Acetamino-ac-tetrahydro-1-naphthoic acid had an m.p. of 186-187° after repeated recrystallization from aqueous alcohol; it was a colorless substance that was soluble in alcohol and insoluble in ethyl acetate.

4.978 mg substance: 0.268 ml N_2 (19.0°, 729.0 mm). Found %: N 6.04. $C_{13}H_{15}O_3N$. Calculated %: N 6.01.

Ethyl ester of 7-amino-ac-tetrahydro-1-naphthoic acid. 3.0 g of 7-amino-ac-tetrahydro-1-naphthoic acid was heated to boiling for 7 hours with 40 ml of absolute ethyl alcohol and an adequate quantity of concentrated H_2SO_4 (until its reaction was acid with Congo red).

Processing that was identical with that described above for the 5-amino acid yielded the ethyl ester of 7-amino-ac-tetrahydro-1-naphthoic acid as a wholly colorless and odorless, highly viscous oil with a b.p. of 159.5-160° at 2.5 mm; $n_D^{19.5}$ 1.5580.

12.285 mg substance: 0.687 ml N_2 (18.0°, 740.5 mm). 9.225 mg substance: 0.539 ml N_2 (18.0°, 740.5 mm). Found %: N 6.39, 6.67. $C_{13}H_{17}O_2N$. Calculated %: N 6.39.

Decarboxylation of 7-amino-ac-tetrahydro-1-naphthoic acid. 5 grams of 7-amino-ac-tetrahydro-1-naphthoic acid was thoroughly triturated with 10 g of $Ba(OH)_2$ and a small amount of methanol. The mixture was dried, pulverized, and destructively distilled from a Wurtz flask at 20-30 mm pressure. The distillate was extracted with ether, and the ether solution was washed with a potassium hydroxide solution and dried with potassium hydroxide. The ether was driven off, and the residue (2 g) distilled at ordinary pressure, b.p. 270-275°; the substance quickly crystallized after distillation, m.p. 40-45°.

Repeated recrystallization from petroleum ether yielded a minute quantity of a substance with an m.p. of 104-106° that was slightly soluble in petroleum ether and a more highly soluble substance with an m.p. of 38-39°. The melting point of the substance with an m.p. of 38-39° indicated that it was ar-tetrahydro-2-naphthylamine [4] —colorless needles that crystallized from petroleum ether only after deep chilling.

6.900 mg substance: 0.596 ml N_2 (22.0°, 736.0 mm). Found %: N 9.68. $C_{10}H_{13}N$. Calculated %: N 9.52.

The acetyl derivative was prepared by reacting an ether solution of ar-tetrahydro-2-naphthylamine with acetyl chloride in the presence of sodium carbonate. Needles with an m.p. of 105.5-106.5° [5].

8.101 mg substance: 0.522 ml N_2 (23.0°, 736.0 mm). Found %: N 7.20. $C_{12}H_{15}ON$. Calculated %: N 7.40.

The substance with an m.p. of 104-106° referred to above was not refined further owing to the minute quantity available; it apparently was somewhat impure 2-naphthylamine. Its mixed melting point with pure

2-naphthylamine (m.p. 110°) was 106–108°.

Diethylaminoethyl ester of 7-amino-ac-tetrahydro-1-naphthoic acid (hydrochloride). The hydrochloride of the diethylaminoethyl ester of 7-nitro-ac-tetrahydro-1-naphthoic acid was reduced under the same conditions as those used in reducing the hydrochloride of the alkamino ester of 5-nitro-ac-tetrahydro-1-naphthoic acid. 2.6 grams of the alkamino ester of the 7-nitro acid yielded 1.5 g of the alkamino ester of the 7-amino acid.

The hydrochloride of the diethylaminoethyl ester of 7-amino-ac-tetrahydro-1-naphthoic acid consisted of beautiful, minute needles with an m.p. of 113–116° (with slight decomposition). The substance was nonhygroscopic, freely soluble in water, alcohol, acetone, and chloroform, and insoluble in ethyl acetate, ether, and CCl_4.

6.205 mg substance: 0.460 ml N_2 (20.5°, 738.0 mm). 5.925 mg substance: 0.441 ml N_2 (24.5°, 740.0 mm). Found %: N 8.38, 8.31. $C_{17}H_{26}O_2N_2 \cdot HCl$. Calculated %: N 8.58.

5,7-Dinitro-ac-tetrahydro-1-naphthoic acid. a) 13 grams of the ac-tetrahydro-1-naphthoic acid was gradually added to 75 ml of HNO_3 (sp. gr. 1.5) the temperature being kept at 17–20°. The reaction mixture was allowed to stand at room temperature for 40 minutes and then poured over ice. The white precipitate was filtered out the next day. This yielded 18 g of a substance with an m.p. of 158–160°. The yield of the impure dinitro acid was 92% of the theoretical. Recrystallization from toluene yielded 15 g of a substance with an m.p. of 162–164°.

The 5,7-dinitro-ac-tetrahydro-1-naphthoic acid had an m.p. of 167.5–168.5° after having been purified by conversion into an ester and saponification of the latter. Crystals with a greenish tinge soluble in acetone, ether, and acetic acid, sparingly soluble in cold toluene and in chloroform.

6.105 mg substance: 0.579 ml N_2 (18.0°, 732.5 mm). 3.132 mg substance: 5.709 mg CO_2, 1.062 mg H_2O. 4.240 mg substance: 7.715 mg CO_2, 1.446 mg H_2O. Found %: C 49.71, 49.62; H 3.79, 3.82; N 10.73. $C_{11}H_{10}O_6N_2$. Calculated %: C 49.62; H 3.77; N 10.52.

b) 0.5 gram of 5-nitro-ac-tetrahydro-1-naphthoic acid was placed in 10 ml of HNO_3 sp. gr. 1.50. The temperature was kept at +20°. Nitration lasted 15 minutes after which the reaction mixture was poured over ice (about 50 mg of ice). The next day the dinitro acid precipitate was filtered out, m.p. 164–165.5°. Several recrystallizations from toluene yielded 5,7-dinitro-ac-tetrahydro-1-naphthoic acid with an m.p. of 167–167.5°. Its mixed melting point with the 5,7-dinitro-ac-tetrahydro-1-naphthoic acid described above (see the preceding experiment) was 167–168°.

6.185 mg substance: 0.578 ml N_2 (20.0°, 714.5 mm). Found %: N 10.25. $C_{11}H_{10}O_6N_2$. Calculated %: 10.52.

c) 1.1 grams of 7-nitro-ac-tetrahydro-1-naphthoic acid was placed in 10 ml of HNO_3 sp. gr. 1.50. The reaction lasted 15 minutes at room temperature. The customary processing yielded 1.2 g of a substance with an m.p. of 165–167°. After recrystallization from toluene raised the m.p. of the substance to 167–167.5°; it was 5,7-dinitro-ac-tetrahydro-1-naphthoic acid. Its mixed melting point with the 5,7-dinitro-ac-tetrahydro-1-naphthoic acid described above was 167–167.5°.

7.260 mg substance: 0.658 ml N_2 (20.0°, 737.0 mm). Found %: N 10.24. $C_{11}H_{10}O_6N_2$. Calculated %: N 10.52.

Oxidation of 5,7-dinitro-ac-tetrahydro-1-naphthoic acid. 0.7 gram of 5,7-dinitro-ac-tetrahydro-1-naphthoic acid was heated to 145–150° with 16 ml of 40% HNO_3 in a sealed tube for 8 hours. When the reaction was over, the acid solution was evaporated to dryness on a water bath. The residue was a grayish substance that was freely soluble in water and had an m.p. of approximately 210° (with decomposition). The yield was 0.6 g. Several recrystallizations from an ether-ligroin mixture raised the m.p. of the substance to 223–224° (with decomposition). The melting point and analysis of the synthesized substance indicated that it was the 3,5-dinitrophthalic acid described in the literature [6].

5.09 mg substance: 0.477 ml N_2 (22.5°, 750.0 mm). 5.205 mg substance: 0.488 ml N_2 (22.5° 750.0 mm). Found %: N 10.70, 10.70. $C_8H_4O_6N_2$. Calculated %: N 10.94.

The monoethyl ester of 3,5-dinitrophthalic acid was prepared as specified by Beilstein and Kurbatov [6]. 0.25 gram of the 3,5-dinitrophthalic acid we had prepared by oxidizing dinitrotetrahydronaphthoic acid was heated with a small amount of absolute ethyl alcohol that contained anhydrous hydrogen chloride. Heating lasted 5 hours, after which the alcohol was driven off in vacuo. Water was added to the residue, and the precipitate was filtered out, yielding 0.2 g of the monoethyl ester of 3,5-dinitrophthalic acid with an m.p. of 184.5°. Recrystallization from a chloroform-petroleum ether mixture raised the melting point to 185–186°.

<u>Ethyl ester of 5,7-dinitro-ac-tetrahydro-1-naphthoic acid</u>. 22 grams of 5,7-dinitro-ac-tetrahydro-1-naphthoic acid was heated to boiling for 8 hours with 250 ml of absolute ethyl alcohol and 5 ml of concentrated sulfuric acid. After the reaction most of the alcohol was driven off, about 50 ml of water was added to the residue, and the ethyl ester of the dinitro acid that separated out was extracted with ether. The ether solution was washed with a 10% soda solution and then with water. It was dried over anhydrous sodium sulfate, after which the ether was driven off, and the residue recrystallized twice from absolute ethyl alcohol. This yielded 18 g of a colorless substance with an m.p. of 43.5-44.5°, which was readily soluble in ether, benzene, and hot alcohol and sparingly soluble in cold alcohol and in petroleum ether.

7.800 mg substance: 0.680 ml N_2 (21.5°, 738.0 mm). Found %: N 9.85. $C_{13}H_{14}O_6N_2$. Calculated %: N 9.52.

<u>5,7-Dinitro-ac-tetrahydro-1-naphthoyl chloride</u>. 6 grams of 5,7-dinitro-ac-tetrahydro-1-naphthoic acid was heated for 2 hours with 10 ml of thionyl chloride. The excess thionyl chloride was driven off in vacuo, and some petroleum ether was added to the residue. After the solution had cooled, rubbing threw down a white precipitate. The precipitate was filtered out and washed with petroleum ether. This yielded 6 g of a substance with an m.p. of 88-90°.

The 5,7-dinitro-ac-tetrahydro-1-naphthoyl chloride has an m.p. of 89.5-90.5° after recrystallization from a benzene-petroleum ether mixture. Rather freely soluble in benzene, sparingly in ether and petroleum ether.

0.1588 g substance: 0.0831 g AgCl. Found %: Cl 12.94. $C_{11}H_9O_5N_2Cl$. Calculated %: Cl 12.48.

<u>5,7-Diamino-ac-tetrahydro-1-naphthoic acid</u>. 5,7-Dinitro-ac-tetrahydro-1-naphthoic acid was dissolved in 450 ml of methanol. 10 grams of Raney's nickel catalyst was added to the solution, and the mixture was agitated in a hydrogen atmosphere; after the requisite quantity of hydrogen (3860 ml) had been added, the catalyst was filtered out, and the methanol driven off in vacuo; hydrogen or some other inert gas has to be passed through a capillary while the methanol is being driven off in vacuo. This yielded 4.7 g of a brown substance with an m.p. of 172° (with decomposition). The yield was 81% of the theoretical.

After recrystallization from absolute ethyl alcohol the 5,7-diamino-ac-tetrahydro-1-naphthoic acid had an m.p. of 177° (wtih decomposition). Light-yellow crystals, somewhat soluble when heated in methanol or ethyl alcohol, sparingly soluble in the alcohols or in ethyl acetate at room temperature. The alcoholic solutions were oxidized extremely readily by atmospheric oxygen.

5.470 mg substance: 0.660 ml N_2 (20.5°, 733.0 mm). 5.570 mg substance: 0.676 ml N_2 (19.5°, 732.0 mm). Found %: N 13.55, 13.64. $C_{11}H_{14}O_2N_2$. Calculated %: N 13.59.

<u>5,7-Diacetamino-ac-tetrahydro-1-naphthoic acid</u>. 0.5 gram of 5,7-diamino-ac-tetrahydro-1-naphthoic acid was heated to 70-80° for 3 hours with 1 ml of acetic anhydride. The reaction mass was treated with water, throwing down a colorless precipitate of the acetyl derivative. This yielded 0.5 g of a substance with an m.p. of 207-210°.

After recrystallization from aqueous alcohol the 5,7-diacetamino-ac-tetrahydro-1-naphthoic acid consisted of colorless needles with an m.p. of 211.5-212.5° that were readily soluble in alcohol.

6.400 mg substance: 0.550 ml N_2 (20.5°, 733.0 mm). 6.900 mg substance: 0.590 ml N_2 (19.5°, 732.0 mm). Found %: N 9.65, 9.51. $C_{15}H_{18}O_4N_2$. Calculated %: N 9.65.

<u>Decarboxylation of 5,7-diamino-ac-tetrahydro-1-naphthoic acid</u>. A mixture of 2.0 g of 5,7-diamino-ac-tetrahydro-1-naphthoic acid and 4.5 g of Ba (OH)$_2$ was distilled destructively in vacuo (5-15 mm pressure). This yielded about 1 g of a substance that was dissolved in ether, the ether solution being washed with an alkali solution and dried over anhydrous sodium sulfate. The ether was driven off, and the residue (m.p. 73-75°) recrystallized twice from absolute ether, which raised the substance's melting point to 79.5-80°. This is the melting point of <u>ar</u>-1,3-tetrahydronaphthalenediamine [7].

4.04 mg substance: 0.606 ml N_2 (21.5°, 752.0 mm). Found %: N 17.20. $C_{10}H_{14}N_2$. Calculated %: N 17.28.

<u>5-Nitro-ac-tetrahydro-1-thionaphthoic acid</u>. A solution of 4.3 grams of KOH in 40 ml of absolute alcohol was saturated with hydrogen sulfide at -5°. A solution of 7.4 g of 5-nitro-ac-tetrahydro-1-naphthoylchloride in 30-35 ml of absolute benzene was gradually added, during the course of 15 minutes, to the resulting solution of KSH. The reaction was carried out with vigorous stirring at -5 to -2°. Fifteen minutes later the precipitated KCl was filtered out, the solvent driven off in vacuo, and the residue triturated with absolute ether. The precipitated potassium salt of the thio acid was filtered out and dried in vacuo, yielding 7 g of the substance. 0.5 g of the

potassium salt of the thio acid was dissolved in 5 ml of water, and the solution was filtered and acidified with dilute hydrochloric acid. The oil that separated out crystallized rapidly into a solid, nearly colorless substance with an m.p. of 69°.

After recrystallization from alcohol the 5-nitro-ac-tetrahydro-1-thionaphthoic acid was a yellowish crystalline substance with an m.p. of 69.5-70.5°, which was readily soluble in ether and hot alcohol, and sparingly soluble in cold alcohol and water.

0.1330 g substance: 0.1310 g BaSO$_4$. 0.1225 g substance: 0.1195 g BaSO$_4$. Found %: S 13.52, 13.39. C$_{11}$H$_{11}$O$_3$NS. Calculated %: S 13.50.

Ethyl ester of 5-nitro-ac-tetrahydro-1-thionaphthoic acid. 5.5 grams of the potassium salt of 5-nitro-ac-tetrahydro-1-thionaphthoic acid was dissolved in 10 ml of absolute ethyl alcohol, about 5 ml of ethyl iodide was added to the solution, and the mixture was heated for an hour on a water bath at 60-70°. After all the KI had been precipitated, the solution was treated with water and extracted with ether. The ether extract was dried over anhydrous sodium sulfate, after which the ether was driven off and the residue distilled in vacuo.

This yielded 4 g of the ethyl ester of 5-nitro-ac-tetrahydro-1-thionaphthoic acid —a yellowish oil with a b.p. of 175-176° at 1-1.5 mm, which crystallized in the cold.

0.2455 g substance: 0.2221 g BaSO$_4$. Found %: S 12.42. C$_{13}$H$_{15}$O$_3$NS. Calculated %: S 12.07.

7-Nitro-ac-tetrahydro-1-thionaphthoic acid. This was synthesized like the 5-nitro-ac-tetrahydro-1-thionaphthoic acid. A solution of 8 g of the acid chloride of the 7-nitro acid in absolute benzene was added to an alcoholic solution of potassium hydrosulfide (produced by saturating 4.3 g of potassium hydroxide with hydrogen sulfide). Appropriate processing yielded 7 g of the potassium salt of the 7-nitro thio acid.

The 7-nitro-ac-tetrahydro-1-thionaphthoic acid crystallized excellently from alcohol as a yellowish crystalline substance with an m.p. of 74.5-75.5°, which was soluble in ether, benzene, hot alcohol and CCl$_4$, and somewhat soluble in cold alcohol.

0.1749 g substance: 0.1701 g BaSO$_4$. 0.1716 g substance: 0.1665 g BaSO$_4$. Found %: S 13.35, 13.32. C$_{11}$H$_{11}$O$_3$NS. Calculated %: S 13.50.

Ethyl ester of 7-nitro-ac-tetrahydro-1-thionaphthoic acid. This was synthesized, like the 5-nitro isomer, by reacting an alcoholic solution of the potassium salt of the 7-nitro thio acid with ethyl iodide. The ethyl ester of 7-nitro-ac-tetrahydro-1-thionaphthoic acid was a light-yellow oil with a b.p. of 184° at 2-2.5 mm. It could be crystallized in the cold.

0.1791 g substance: 0.1560 g BaSO$_4$. Found %: S 11.96. C$_{13}$H$_{15}$O$_3$NS. Calculated %: S 12.07.

Diethylaminoethyl ester of 7-nitro-ac-tetrahydro-1-thionaphthoic acid (hydrochloride). 3.2 grams of the potassium salt of 7-nitro-ac-tetrahydro-1-thionaphthoic acid was dissolved in 40 ml of absolute ethyl alcohol, 1.71 g of the hydrochloride of diethylamino-ethyl chloride was added to the solution, and the mixture was heated to 60-70° for 4 hours. The precipitated potassium chloride was filtered out, and the alcohol was then driven off in vacuo. The residue was treated with a 10% soda solution, and the base of the alkamino ester was extracted with ether. The ether solution was dried over anhydrous sodium sulfate, and a solution of hydrogen chloride in absolute ether was added, throwing down the hydrochloride of the alkamino ester. This yielded 3.3 g of a substance with an m.p. of 144-147°.

Reprecipitation from alcohol by ether yielded the hydrochloride of the diethylaminoethyl ester of 7-nitro-ac-tetrahydro-1-thionaphthoic acid as a coloress, nonhygroscopic substance with an m.p. of 147.5-149°, soluble in water and alcohol, and insoluble in ether.

0.1060 g substance: 0.0653 g BaSO$_4$. 5.710 mg substance: 0.400 ml N$_2$ (19.5°, 724.0 mm). Found %: S 8.46; N 7.80. C$_{17}$H$_{24}$O$_3$N$_2$S · HCl. Calculated %: S 8.59; N 7.51.

SUMMARY

1. Nitrating ac-1-tetrahydronaphthoic acid with nitric acid, sp. gr. 1.5, yields 5,7-dinitro-(1,2,3,4-tetrahydro)-1-naphthoic acid, while nitration with nitric acid, sp.gr. 1.4, yields a mixture of two mononitro acids: 5- and 7-nitro-(1,2,3,4-tetrahydro)-1-naphthoic acid; a method is set forth for separating these mononitro acids.

2. The structure of the synthesized nitro acids is established by converting them into compounds of known structure.

3. Catalytic reduction is employed to secure the respective diamino and amino-ac-1-tetrahydronaphthoic acids from the dinitro and mononitrotetrahydronaphthoic acids.

4. The simplest derivatives of all the nitro (amino)-ac-1-tetrahydronaphthoic acids have been synthesized.

5. 5 (7)-Nitro-ac-1-tetrahydrothionaphthoic acids and some of their derivatives have been synthesized.

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THE ALKALOIDS OF THALICTRUM MINUS L.

II. THE STRUCTURE OF THALICMIDINE AND THALICMINE

S. Yunusov and N. N. Progressov

We have already reported [1] that in our investigation of the above-ground parts of Thalictrum minus L. we succeeded in isolating two alkalids (thalmine and thalmidine), while the roots of this plant yielded three bases (thalicmine, thalicmidine, and Base No. 5). Thus we have secured five new alkaloids in crystalline form from the whole of the plant Thalictrum minus L. Some of the physicochemical properties were given for four of the alkaloids, together with their incomplete structural formulas. These findings led us to postulate that these alkaloids are derivatives of tetrahydroisoquinoline.

In the course of further research on thalicmidine we were able to confirm this hypothesis experimentally and to establish conclusively that aporphine is the parent substance of this alkaloid. Now, this base contains two less hydrogen atoms than was reported earlier [1], i.e., thalicmidine is $C_{20}H_{23}NO_4$. What we still had to determine was the function of the fourth oxygen atom. We found that this oxygen atom possesses weak phenolic properties, inasmuch as thalicmidine dissolves in dilute alkalies and is extracted from alkaline solution completely by ether; diazomethane does not methylate it even when used in considerable excess. Hence, the formula of thalicmidine may be depicted as $C_{16}H_{16}(NCH_3)(OH)(OCH_3)_3$. Reaction with acetic anhydride yields an optically inactive substance that has no basic properties, which we oxidized with nitric acid (sp. gr. 1.34). This reaction yielded mellophanic acid, as was confirmed by securing the crystalline tetramethyl ester of that acid. All the foregoing reactions lead to the conclusion that the basic skeleton of thalicmidine is aporphine.

The one thing that was left to establish the structure of thalicmidine was fixing the position of the substituent groups. As we know, all tetrasubstituted aporphine alkaloids known up to the present are derivatives of two types of tetrahydroxyaporphine (I and II).
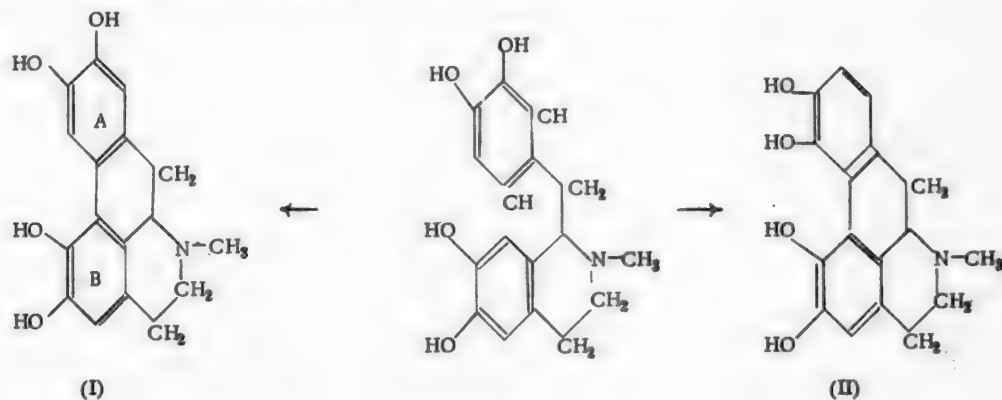
One of the present authors has discovered some general properties of alkaloids of the aporphine group that facilitate determination of the position of the substituent groups.

1. No mellophanic acid is produced when the product of the action of acetic anhydride upon alkaloids that have no substitutents in the A and B benzene rings is oxidized with strong nitric acid. Instead, benzenedi- or tricarboxylic acid is produced, depending upon the positions of the substitutents in one of these rings.

2. Alkaloids that are aporphine derivatives possessing substituent groups at the 2,3,5,6 and 3,5,6 positions have a specific rotatory power (40-100°) that is much smaller than that of bases having substituents at the 3,4,5,6 and 4,5,6 position (200-300°).

3. This group is almost always located at the 5 and 6 positions in all aporphine alkaloids that contain a methylenedioxy group.

4. Hydroxyl groups at the 5 and 6 positions are weakly phenolic.

Inasmuch as the $[a]_D -84.05°$, the hydroxyl group is weakly phenolic, and oxidation yields mellophanic acid, the foregoing rules indicate that thalicmidine must have the structure (III) [3]:


(III)   (IV)
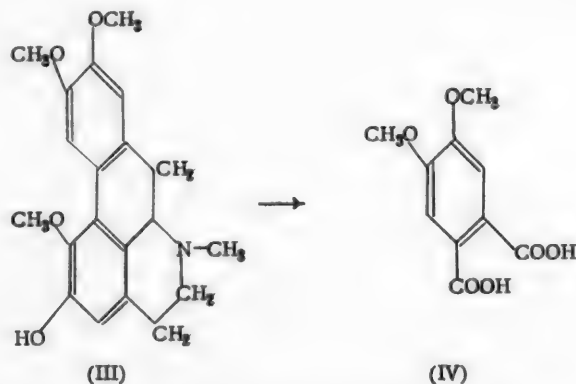
The fact that we secured metahemipinic acid (IV) by oxidizing thalicmidine with potassium permanganate is partial confirmation of this structure. It follows that the two methoxy groups occupy the 2 and 3 positions.

We secured further experimental evidence in support of the correctness of the formula (III) by carrying out a Hofmann decomposition of the methyl ester of thalicmidine. After finding that we could not methylate the hydroxyl group of thalicmidine with diazomethane, we secured the methiodide of the methyl ester of thalicmidine (V) by reacting the latter with methyl iodide in a dilute alkaline medium. M.p. 221-222°. Heating the methiodie (V) with an alcoholic (methyl) alkali produced a high yield of the crystalline, optically inactive des-N-methyl-O-methylthalicmidine (VI) with an m.p. of 72-73.5°. Its hydrochloride had an m.p. of 255-257°.

The des-base (VI) yields an easily and excellently crystallizing methiodide (m.p. 280°), which breaks down into trimethylamine and the crystalline tetramethoxyvinylphenanthrene (VII) (m.p. 143°) when heated with an alcoholic alkali:

(V)   (VI)
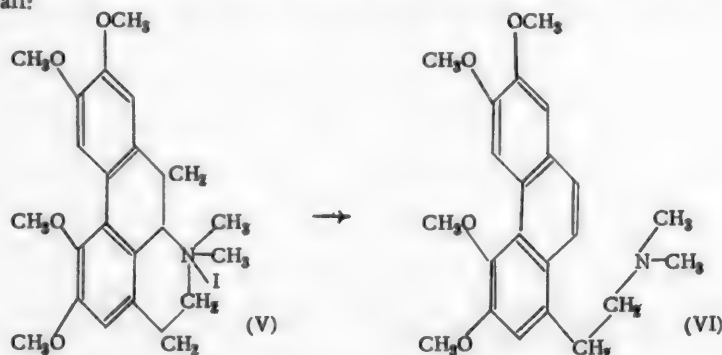
When the non-nitrogenous substance (VII) was oxidized with potassium permanganate in acetone solution, we obtained the corresponding crystalline monocarboxylic acid (VIII), with an m.p. of 218°. It follows that the only possible structure for the methyl ester of thalicmidine is (IX):

(VII) → (VIII) (IX)
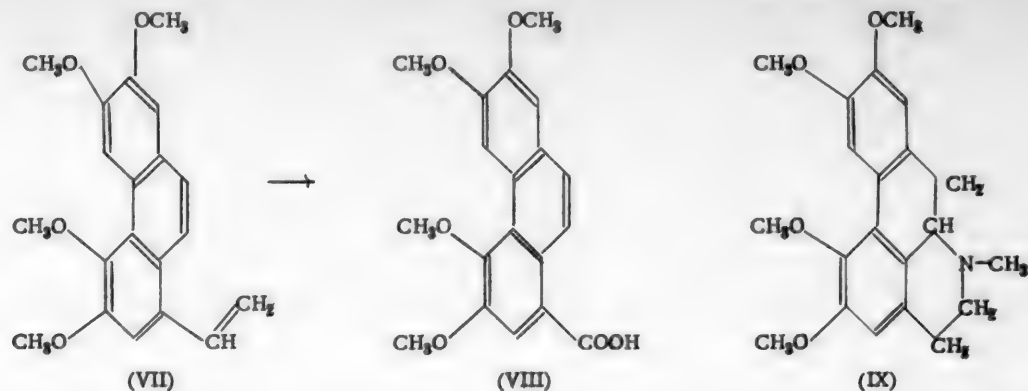
The properties and formula of methylthalicmidine (IX) established by us agree almost completely with the properties of glaucine (IX) [4], O-dimethylboldine (IX) [5], and their derivative and decomposition products (see the table):

TABLE

Name of substance	O-Methylthalic-midine	Glaucine	O-Dimethyl-boldine
Methiodidide	221-222°	222°	221°
Methiodide of the des-bas	276-280	278-280	276-280
Tetramethoxyvinylphenanthrene	143	142	143
Tetramethoxyphenanthrenecarboxylic acid	218		214

For want of glaucine or boldine, we were unable to identify them conclusively immediately. But all the facts cited above prove that O-methylthalicmidine (IX) is identical with glaucine and O-dimethylboldine. On the basis of certain phylogenetic considerations set forth by one of the present authors in his article entitled " The dynamics of the accumulation, the role, and the formation of alkaloids in plants" [6], we assumed that Thalictrum minus L. must contain O-methylthalicmidine, i.e., glaucine, depending upon its period of growth and habitat. As a matter of fact, glaucine has been isolated from the nonphenolic portion of the alkaloids obtained from the roots of Thalictrum minus L. gathered (on May 23-28, 1949) in the stage of unripe fruit (in Kuyan-sae, Kulsu landmark, Zaaminsk District, Usbek S.S.R.). We have thus been able to confirm the formula for O-methylthalicmidine (IX) conclusively by making direct determinations of the mixed melting points of their methiodides and des-products.

It should be noted that the Hofmann decomposition of thalicmidine and of its methyl ester normally takes place along only one of the theoretically possible lines, yielding the crystalline, optically inactive des-N-methyl-thalicmidine (m.p. 252-253°). The hydroxyl group retained in the last substance is likewise weakly phenolic.

Before commencing further research into the structure of thalicmine, we checked whether that alkaloid belonged to the N-methylbenzyltetrahydroisoquinoline series. We found [1] that reacting thalicmine with acetyl chloride yielded an optically inactive crystalline substance that had no basic properties (XIII). Further, by oxidizing this substance with strong nitric acid we obtained the tetracarboxylic acid (XIV), whose mixed melting point with mellophanic acid, as well as that of their tetramethyl esters, exhibited no depression. Moreover, by . distilling the synthesized optically inactive monoacetylthalicmine with zinc dust, we isolated an adequate percentage of phenanthrene (XV) from the reaction products. These reactions clearly show that thalicmine does not belong to the benzyltetrahydroisoquinoline series, but rather to a related one, the aporphine series. Hence the amount of hydrogen it contains, which is hard to determine from the analytical data, becomes clear: the composition of thalicmine is $C_{21}H_{23}NO_5$.

Thalicmine is a tertiary base that contains an NCH_3 group. Three oxygen atoms are contained in methoxy groups, the two others being in a methylenedioxy group: $C_{16}H_8(NCH_3)(OCH_3)_3(CH_2O_2)$. Thalicmine is decomposed readily and smoothly in a Hofmann reaction. Repeating the decomposition twice by reacting the methiodide with a 30 % KOH solution in methanol yields trimethylamine and a nonnitrogenous substance.

Des-N-methylthalicmine (XI) $C_{22}H_{23}NO_5$ is optically inactive and have an m.p. of 150-151°. The m.p. of its sulfate is 127-128°, of its methiodide 236-237°. No matter how often we repeated the Hofmann decomposition we always obtained the optically inactive des-N-methylthalicmine almost exclusively. It follows that the decomposition proceeds along one of the theoretically conceivable lines.

The non-nitrogenous substance, $C_{19}H_{18}O_5$ (XII), had an m.p. of 185-186°. All the cited reactions with thalicmine prove convincingly that it belongs to the series of aporphine alkaloids.

Thus, thalicmine is the first instance in which alkaloids of the aporphine group have been found in the plants of the Ranunculaceae family we have studied, as well as the first pentahydroxy substituted aporphine ever discovered. The patterns set forth above for the position of the substituent groups in alkaloids of the aporphine series and the analogy with the alkaloids of the narcotine type lead us to assume that thalicmine is 3,4,7-tri-methoxy-5,6-methylenedioxyaporphine (X) [3]. The decomposition of thalicmine we carried out may be summarized as follows:
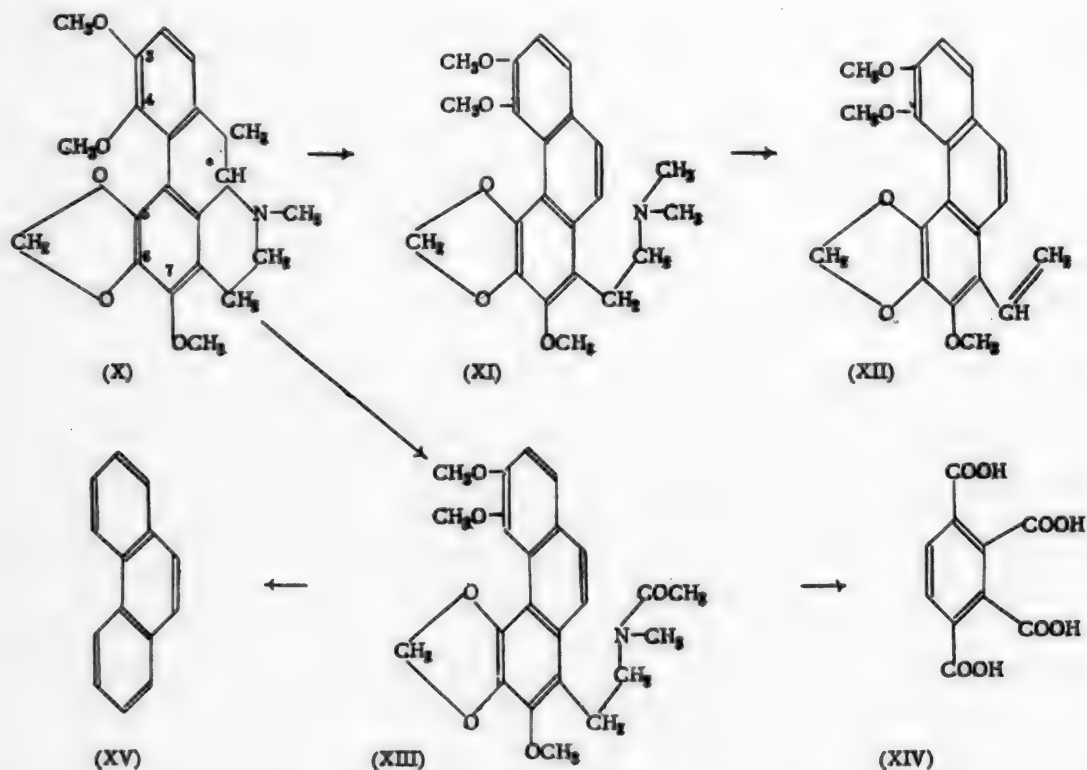
EXPERIMENTAL

Mellophanic acid from thalicmidine. 1.2 grams of thalicmidine was dissolved in 7 ml of acetic anhydride and boiled for one hour. After all the anhydride and acetic acid had been evaporated in a dish on a water bath, what was left was a noncrystalline mass that exhibited no basicity or optical activity. The residue was evaporated 5 times with 8 ml portions of nitric acid (sp. gr. 1.34) on a water bath. The resultant yellow amorphous residue was recrystallized from strong nitric acid. The crystalline acid, with an m.p. of 233-236°, exhibited no depression of the melting point when mixed with the mellophanic acid secured from thebenine. Nor did the mixed melting point (134°) of the tetramethyl esters of these acids, prepared by methylating them with diazomethane, exhibit any depression.

Oxidation of thalicmidine. 1.3 grams of the base, with an m.p. of 192-193°, was dissolved in 15 ml of 2% hydrochloric acid. Then the solution was neutralized and stirred mechanically while a 3% solution of $KMnO_4$

(9.9 g in 300 ml of water) was added. The whole of the permanganate solution (24 atoms of oxygen) was added in the space of two hours. Then the solution was heated to 40° for one hour. The unreacted permanganate was decolorized by adding pulverized Na$_2$SO$_3$. The solution was filtered, the manganese dioxide being transferred to a flask, boiled with water, and re-suction-filtered. The filtrates (500 ml) were combined. The solution was extracted with ether after it had been acidified with strong hydrochloric acid. After it had been dried and the ether driven off, the mass crystallized as minute yellow-orange needles. The yield was 0.8 g. Dissolving in alcohol and adding freshly distilled aniline instantaneously yielded the anilide with an m.p. of 168-169°. The m.p. was raised to 170-171° (with decomposition) by recrystallization from absolute alcohol. Its mixed melting point with metahemipin-anilide, prepared from salsolidine, exhibited no depression, all three samples fusing simultaneously at 170-171° (with decomposition).

Methiodide of O-methylthalicmidine. 20 ml of methanol was poured over 2 g of thalicmidine ground to a powder, and 0.4 g of powdered KOH was added. The whole dissolved, the solution turning dark. 1 ml of methyl iodide was added to the flask contents, and the mixture was refluxed one hour. After the contents had cooled, another 1 ml of methyl iodide was added, the mixture was again refluxed for 2 hours and left to stand for 14 hours. Crystals settled out of the methanol partially. The solution was neutralized with litmus paper. The solvent was evaporated to a volume of 10 ml, which increased the quantity of crystals, the whole mass crystallizing when a rod was used for rubbing. The crystals were suction-filtered and washed with methanol. Recrystallization from water yielded minute acicular crystals with an m.p. of 221-222°. The yield was 2.2 g.

Des-O-methyl-N-methylthalicmidine. 2.2 grams of the methioidide of O-methylthalicmidine was ground to a powder and transferred to a flask that contained 25 ml of 30% KOH (7.5 g) in methyl alcohol. After the mixture had been boiled for 3 hours, the methanol was driven off, and evaporation was continued in a dish. The adding of water caused a yellow resinous mass of the des-base to float to the surface; it was separated and washed with water. The des-base, purified via its hydrochloride, consisted of lustrous silvery crystals with an m.p. of 255-257°. 1.4 grams of the hydrochloride of the des-base was dissolved in 100 ml of water and decomposed with 20% ammonia. This yielded the des-base as crystalline flocs (when less water was used, an oily mass settled out, which solidified upon standing). The m.p. was 72-73.5° after suction-filtering, washing with water, and drying, while the oily portion yielded a product with an m.p. of 69-71°. The m.p. was 72-73.5° after recrystallization from petroleum ether (b.p. 60-80°).

0.0224 g substance: 13.3 ml 0.1 N Na$_2$S$_2$O$_3$. 0.0230 g substance: 14.4 ml 0.1 N Na$_2$S$_2$O$_3$. Found %: OCH$_3$ 31.31, 33.01. C$_{22}$H$_{27}$NO$_4$. Calculated %: OCH$_3$ 33.33.

Methiodide of des-O-methyl-N-methylthalicmidine. 0.6 gram of des-O-methyl-N-thalicmidine, with an m.p. of 72-73.5°, was dissolved in 20 ml of acetone, and 1 ml of methyl iodide was added to the solution. The crystals of the methiodide settled out at once. After standing for an hour they were suction-filtered and washed with acetone. This yielded 0.7 g of snow-white methiodide with an m.p. of 271-274°, slightly soluble in water. The m.p. was raised to 276-280° (with decomposition) by recrystallization from alcohol.

2,3,5,6-Tetramethoxy-8-vinylphenanthrene. 0.7 gram of the methiodide of des-O-methyl-N-methylthalic-midine was ground to a powder and added to a solution of 12.5 ml of 30% KOH (3.75 g) in methanol. The mixture was boiled, trimethylamine being given off and a nonnitrogenous substance being formed. The methanol was evaporated, water was added to the residue, and the product was extracted with ether. The ether solution was washed with 10% sulfuric acid and with water. Drying and driving off the ether yielded crystals of the non-nitrogenous substance with an m.p. of 138-140°. The m.p. was raised to 143° by recrystallization from alcohol. 0.4 g yield.

0.0236 g substance: 18.1 ml 0.1 N Na$_2$S$_2$O$_3$. 0.0232 g substance: 16.4 ml 0.1 N Na$_2$S$_2$O$_3$. Found %: OCH$_3$ 40.67, 37.28. C$_{20}$H$_{20}$O$_4$. Calculated %: OCH$_3$ 38.27.

2,3,5,6-Tetramethoxyphenanthrene-8-carboxylic acid. 0.2 gram of 2,3,5,6-tetramethoxy-8-vinylphenan-threne was dissolved in 50 ml of acetone and then oxidized with a solution of KMnO$_4$ (0.25 g) in 50 ml of acetone. The permanganate was added in small portions during the course of 2 hours, with constant stirring, to the reaction mass, which was kept at 25°. After all the permanganate had been decolorized, the manganese dioxide was filtered out and washed, first with acetone and then with hot water. After the acetone had been evaporated the mass crystallized in part. The aqueous solution was evaporated on a bath. The mass recovered after the acetone and the water had been driven off was acidified with 10% hydrochloric acid and extracted

with ether. The ether solution was washed first with 20 ml of 10% NaOH and then with water, after which the solution was dried and the ether was driven off. The residue was a small quantity of resinous substance. The alkaline solution and the wash waters were acidified with 10% hydrochloric acid and extracted with ether. Drying, followed by driving off the ether, yielded the acid as small crystalline needles with an m.p. of 208°. The m.p. was 218° after recrystallization from alcohol.

Recovery of glaucine. Extracting 43 kg of the roots of Thalictrum minus L., harvested during the unripe fruit stage (July 23-28, 1949), yielded 368.3 g (0.85%) of total ether-soluble alkaloids. 111.2 grams of the technical hydrobromide, with an m.p. of 220-233°, was obtained from an acetone solution of the nonphenolic portion of the total alkaloids, the m.p. being raised to 235-237° by recrystallization from water. Reacting an aqueous solution of 1 g of the hydrobromide (m.p. 235-237°) with 25% ammonia yielded an amorphous base, which soon began to turn yellow. After being washed with water and dried, the base was ground to a powder with an m.p. of 89-90°. After recrystallization from ether, the m.p. was 104-109°; $[a]_D$ + 84°.

The methiodide was secured by dissolving 0.8 g of the base in 10 ml of acetone, and adding 1 ml of methyl iodide and refluxing the mixture for 1.5 hours. The finely crystalline methiodide was suction-filtered and washed with acetone. M.p. 216-219°. Yield 0.9 g. Its mixed melting point with crystals of the methiodide of O-methyl-thalicmidine exhibited no depression.

Performing a Hofmann decomposition reaction under the same conditions as those employed for the O-methyl thalicmidine (30% alcoholic solution of KOH), we secured the des-N-methyl base, with an m.p. of 63-68°, in the first stage. The m.p. was raised to 70-72° by recrystallization from petroleum ether (b.p. 40-60°). The mixed melting point with des-methyl-O-methylthalicmidine exhibited no depression, nor did the mixed melting point of their hydrochlorides (m.p. 256-257°).

The second stage of the Hofmann decomposition reaction was performed with the technical methiodide (m.p. 262-265°). This yielded trimethylamine and a nonnitrogenous crystalline substance with an m.p. of 134-136°. The m.p. was raised to 141-142° by recrystallization from alcohol. The yield was 0.45 g. The mixed melting point with the crystals of the nonnitrogenous product obtained from O-methylthalicmidine exhibited no depression.

Mellophanic acid from Thalicmine. Boiling 1.5 g of thalicmine in 10 ml of acetic anhydride yielded 1.45 g of crystalline N-acetylthalicmine, with an m.p. of 191-192°. This substance was not basic and was optically inactive. Subsequent oxidation with strong nitric acid and identification of the acids and of their esters were effected as in the case of thalicmidine.

Distillation of N-acetylthalicmine with zinc dust. 2.6 grams of N-acetylthalicmine was mixed with 26 g of zinc dust. Then the mixture was wetted with alcohol and sawed into pieces. The mass was dried at 100° and then the pieces were charged into a refractory tube and covered with a layer of asbestos. The tube was placed at a slant in a Liebig electric furnace. Distillation in a current of hydrogen lasted 25 minutes. The contents of the receiver and the tube were washed with ether. The ether solution was washed, first with 30 ml of 10% hydrochloric acid and then with 30 ml of 2% KOH and water, after which it was dried over calcined sodium sulfate. After the ether had been driven off to small volume, the residue was transferred to a small flask, where the phenanthrene partially crystallized. The yield was 0.6 g.

Des-N-methylthalicmine. 2.5 grams of the crystalline methiodide with an m.p. of 235-237° was placed in a flask containing 25 ml of a 30% solution of KOH (7.5 g) in methanol, and the mixture was boiled for 2 hours. Then the solution was driven off. The des-N-methylthalicmine remained insoluble when water was added. The crystals were suction-filtered and washed with water. The aqueous-alkaline solution (orange-colored) was extracted exhaustively with ether. After the ether had been driven off, the crystals produced were combined with the bulk of the crystals of the des-N-methyl base. The yield was 1.7 g, the m.p. 145-149°.

The 1.7 g of the technical des-base was recrystallized from methanol, (1:15). This yielded 1.2 g of minute acicular colorless crystals (flocs), with an m.p. of 150-150.5°. Des-N-methylthalicmine is optically inactive.

0.1242 g substance: 0.3176 g CO_2; 0.0774 g H_2O. 0.1299 g substance: 0.3262 g CO_2; 0.0768 g H_2O. 0.1346 g substance: 0.3395 g CO_2; 0.0820 g H_2O. 0.1106 g substance: 3.8 ml N_2 (19°, 727.92 mm). 0.1134 g substance: 3.9 ml N_2 (17.7°, 733.58 mm). Found %: C 69.23, 68.53, 68.83; H 6.92, 6.61, 6.82; N 3.76, 3.82. $C_{22}H_{25}NO_5$. Calculated %: C 68.93; H 6.52; N 3.65.

Des-N-methylthalicmine sulfate. When the des-base was mixed with 10% sulfuric acid, the sulfate was produced as shiny little lamellae. The m.p. was 127-128° (with decomposition) after recrystallization from water, and 125-127° (with decomposition) from alcohol. The isolated crystalline base had an m.p. of 149-150°.

Des-N-methylthalicmine methiodide. 1.3 gram of des-N-methylthalicmine was dissolved in 20 ml of methanol, and 2.3 g of methyl iodide was added. After a brief period (5 minutes) of gentle heating the crystals of the methiodide were formed, absorbing all the solvent. The mass was boiled for 2 hours and cooled, the crystals being suction-filtered, washed with methanol, and dried. The methiodide consisted of minute acicular, snow-white crystals with an m.p. of 236-237° (with decomposition) in a sealed capillary. The yield was 1.2 g.

The nonnitrogenous product $C_{20}H_{16}O_5$. 9 grams of KOH was dissolved in 30 ml of methanol, 1.7 g of des-N-methylthalicmine methiodide was added to the solution, and the mixture was refluxed. Trimethylamine began to be given off within 15 minutes. The mixture was refluxed for 4 hours. Then the contents of the flask were transferred to a dish and evaporated on a water bath. When water was added, the nonnitrogenous substance floated to the surface as lustrous crystals. The whole mass was transferred to a separatory funnel and extracted with ether. We collected 1 liter of a faintly yellow ether solution. The ether solution was filtered and washed with 25 ml of a 5% solution of hydrochloric acid. The acid solution reacted weakly with silicotungstic acid. The ether solution was rewashed with water, filtered, and dried over sodium sulfate. When the solution was evaporated to a volume of 50 ml, crystals began to settle out of the still-boiling ether as lustrous flakes. The crystals were suction filtered and washed with ether. M.p. 185-186°. The yield was 0.4 g.

0.1224 g substance: 0.3164 g CO_2; 0.0614 g H_2O; 0.1200 g substance: 0.3074 g CO_2; 0.0618 g H_2O. 0.0288 g substance: 12.0 ml 0.1 N $Na_2S_2O_3$; 0.0228 g substance: 12.0 ml 0.1 N $Na_2S_2O_3$. Found %: C 70.54, 71.68; H 5.61, 5.71; OCH_3 27.86, 28.09. $C_{20}H_{16}O_5$. Calculated %: C 70.97; H 5.32; OCH_3 27.51.

SUMMARY

1. Determination of the functional groups has made it possible to portray the formula of thalicmidine, $C_{20}H_{23}NO_4$, as follows: $C_{16}H_{10}(NCH_3)(OCH_3)_3(OH)$; the last hydroxyl group is weakly phenolic. The hydroxyl group retained in des-N-methylthalicmidine is likewise weakly phenolic.

2. Mellophanic acid is formed when the substance obtained from thalicmidine by boiling the latter in acetic anhydride is oxidized. Oxidation of thalicmidine itself yields metahemipinic acid.

3. Repeating the Hofmann decomposition of O-methylthalicmidine twice yields a nonnitrogenous substance, which yields tetramethoxyphenanthrenecarboxylic acid upon oxidation.

4. In the unripe fruit stage the roots of Thalictrum minus L. contain d-glaucine. The latter has been identified as O-methylthalicmidine.

5. The structure of thalicmidine is that of 2,3,5-trimethoxy-6-hydroxyaporphine.

6. Mellophanic acid and phenanthrene have been obtained from N-acetylthalicmine, which is neither optically active nor basic.

7. Repeating the Hofmann decomposition reaction of thalicmine twice yielded trimethoxymethylenedioxyvinylphenanthrene.

8. Thalicmine is a derivative of pentahydroxyaporphine. Its structure is apparently that of 3,4,7-trimethoxy-5,6-methylenedioxyaporphine.

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THE ALKALOIDS OF HAPLOPHYLLUM PERFORATUM, H. PEDICELLATUM, H. DUBIUM, H. BUCHARICUM, AND H. VERSICOLOR. I.

S. Yunusov and G. P. Sidyakin

The genus Haplophyllum A. Iuss. (Rutaceae family) embraces 32 species of plants that grow on the territory of the Soviet Union, 23 of them being found in Central Asia, including 14 in Uzbekistan [1]. The Rutaceae family includes the thoroughly investigated Citrus genus and the Pilocarpus jaborandi plant, which contains the valuable alkaloid pilocarpin. Representatives of the Haplophyllum genus, however, have remained practically unexplored chemically. All we have is some information on the approximate alkaloid content of some species in this genus [2], and the report that the alkaoid haplophylline $C_{16}H_{23}NO_4$ has been isolated from H. Sierversii [3]. We have been unable to find any further information on this alkaloid in the literature. Research on the alkaloid-containing species of the Haplophyllum genus is, therefore, of indisputable interest. With this in mind, we set as our objective an investigation of the Haplophyllum species that grow on the territory of Central Asia [4].

A 1948 botanical expedition of the Institute of Chemistry of the Uzbek Academy of Sciences, headed by E. E. Korotkova (and with one of the present authors as a member — G.P.S.), discovered and collected several alkaloid-containing species of the Haplophyllum A. Iuss. genus in the Kashka-Darya and Surkhan-Darya regions of Uzbekistan. We made the most detailed analysis of the plant Haplophyllum perforatum (M.B.) Kar. et Kir. (synonyms Ruta divaricata Siev., H. Sieversii, Fisch). We also began a study of the alkaloids in H. pedicellatum Bge. (synonyms H. hirsutum Rgl. et Schmalh., H. pilosum Franch.), H. dubium Eug. Kor. (synonyms H. Alberti Regelii f. subternata Eug. Kor.), H. bucharicum Litv. (synonym H. nigripes Nevski), and H. versicolor Fisch. et Mey (synonyms H. lasianthum Bge, H. hispidulum Bge.).

1. H. perforatum was collected in the vicinity of the villages Varganza and Makrida, Kitab district, Kashka-Darya region (the western spurs of the Zeravsnan range, basin of the Kashka-Darya river). In this region this plant grows on the partially bare slopes of the foothills and the lower mountain zones.

The alkaloids were extracted from the leaves and the small stems of H. perforatum, gathered during the budding period, with dichloroethane, the bases being extracted from the latter by means of dilute sulfuric acid. When the acid solution was alkalinized with gaseous ammonia, the bases were precipitated (aqueous mother liquor "A"). The precipitate was recrystallized from benzene and then from acetone. This yielded the hydrochloride, from which the bases were recovered as microscopic needles with an m.p. of 155-156°. This base is optically inactive, freely soluble in chloroform, less so in benzene and ether, and slightly soluble in water and petroleum ether; it crystallizes from acetone (1: 15) and alcohol as minute needles. The yield was 0.075% (of the weight of the dry leaves). Elementary analysis indicated that its empirical formula was $C_{17}H_{19}NO_6$. Since this alkaloid proved to differ from all the bases described in the literature up to now, we named it haploperine.

Haploperine is a weak base, its salts hydrolyzing readily in aqueous solutions, even in the cold. It is an unsaturated compound, decolorizing permanganate in an acid medium instantaneously; it contains two methoxy groups, but no methylenedioxy group. The base does not dissolve in caustic alkalies; it forms a crystalline hydrochloride. When haploperine is heated for a long time with an alcoholic alkali, all of it is recovered unchanged. When haploperine is heated with 20% hydrochloric or 25% sulfuric acid, it yields a crystalline product — colorless needles with an m.p. of 138-139°. This product crystallizes from alcohol (1:7), is insoluble in caustic alkalies, and decolorizes permanganate in acid media; it retains both of the methoxy groups, but has no hydroxyl group. It is most likely that in this reaction one molecule of water is split off, since the elementary analysis indicates that the minimum formula of the base has been diminished by one atom of oxygen and two atoms of hydrogen. The mother liquors contained no other products besides the substance with an m.p. of 138-139°.

Haploperine is not affected by boiling with methyl iodide. But when it is heated in a sealed tube immersed

Minute, slightly grayish crystals settled out; they were suction-filtered, washed with ether, and dried <u>in</u> vacuo. The yield totaled 0.8 g. M.p. 123-125°; the mixed melting point with the original base was 113-115°. The m.p. was raised to 138-139° by triple recrystallization from alcohol (1:7). The action of 25% sulfuric acid upon 1 g of the base, using the same procedure as before, yielded 0.6 g of a crystalline substance, which proved to be the same as the product secured by the hydrochloric acid treatment. We were unable to isolate any other reaction products.

0.112 g substance: 0.2658 g CO_2; 0.602 g H_2O. 0.1262 g substance: 0.3006 g CO_2; 0.0672 g H_2O. 0.0798 g substance: 3.2 ml N_2 (16°, 725.9 mm). 8.685 mg substance: 0.346 ml N_2 (23°, 736 mm). 0.226 g substance: 8.5 ml 0.1 N $Na_2S_2O_3$ (Viebock). 0.0223 g substance: 8.3 ml 0.1 N $Na_2S_2O_3$.
Found %: C 65.23, 65.00; H 6.06, 5.96; N 4.43, 4.45; CH_3O 19.13, 18.94. $C_{17}H_{17}NO_5$.
Calculated %: C 64.76; H 5.39; N 4.44; $2CH_3O$ 19.55.

Isohaploperine. 1 ml of methyl iodide was added to 1 g of the base dissolved in 30 ml of acetone, and the mixture was boiled for 6 hours on a water bath. The solution was filtered and concentrated to 5 ml. Minute crystals, which turned out to be the original base, settled out overnight. 1 gram of the base was mixed with 2 ml of methyl iodide (using no solvent), and the mixture was heated on a boiling water bath in a sealed tube for about an hour. The base began by dissolving, crystals appearing on the walls of the tube as heating continued. The contents of the tube solidified completely upon cooling. The tube was opened, and the residual methyl iodide was driven off, leaving a solid, faintly-colored residue. The yield was 1.0 g. The isohaploperine produced was dissolved by heating it in 6 ml of methanol, large needles settling out when the latter cooled. Recrystallization was repeated three times, after which the isohaploperine had an m.p. of 158-159°; its mixed melting point with the original base was 132-134°.

0.242 g substance: 4.8 ml 0.1 N $Na_2S_2O_3$ (Viebock). 0.0252 g substance: 4.9 ml 0.1 N $Na_2S_2O_3$.
Found %: CH_3O 10.09, 9.90. $C_{17}H_{19}NO_6$. Calculated %: CH_3O 9.84.

Hydrogenation of haploperine. 1 gram of haploperine with an m.p. of 155-156° was dissolved in 20 ml of acetic acid and reduced with a platinum catalyst, prepared (by the Adams method) from 0.21 g of platinic oxide. The absorption of 205 ml of hydrogen took 1 hour and 20 minutes (67 ml of hydrogen being required for one double bond). No more hydrogen was absorbed during further shaking on the agitator. The catalyst was suction-filtered and washed with water. The filtrate and the wash waters were combined. The acid solution was alkalinized with 25% ammonia. This threw the base down as a precipitate, which was suction-filtered and washed, first with 15 ml of water, then with 3 ml of alcohol, and then with 5 ml of ether. The m.p. was 159-160° after drying in the vacuum desiccator. The yield was 0.9 g. The melting point was unaffected by recrystallization from acetone (1:20).

Hexahydrohaploperine was slightly soluble in water, ether, and petroleum ether, more readily soluble in alcohol, and freely soluble in chloroform. We were unable to secure the perchlorate, the hydrochloride, the picrate, the oxalate, the hydriodide, the nitrate, or the sulfate in the crystalline state under ordinary conditions.

Skimmianine. 35 grams of the thick oil obtained from the aqueous mother liquor "A" was boiled with 600 ml of a 1:3 mixture of acetone and petroleum ether. The solution was filtered hot; during the next 24 hours crystals mixed with a yellow oil settled out. The solvent was evaporated to dryness. 125 ml of ether was added to the residue, the crystals not dissolving, though the oil dissolved completely. The crystals were suction-filtered and washed with ether (mother liquor "B"). The yield was 6 g. Triple recrystallization from methanol (1:5) yielded large, colorless needles with an m.p. of 175-176°.

0.1062 g substance: 0.2504 g CO_2; 0.0504 g H_2O. 0.1032 g substance: 0.2442 g CO_2; 0.0502 g H_2O. 0.0928 g substance: 4.6 ml N_2 (17°, 715 mm). Found %: C 64.34, 64.57; H 5.31, 5.44; N 5.37. $C_{14}H_{13}NO_4$. Calculated %: C 64.86; H 5.0; N 5.4.

The picrate of skimmianine was prepared by mixing together alcoholic solutions of the base of picric acid, minute crystals with an m.p. of 187-188° settling out. The crystals had an m.p. of 195-197° (with decomposition) after triple recrystallization from alcohol.

Processing the mother liquor "B". The ether mother liquor "B" left after the skimmianine had been filtered out was concentrated to small volume and poured into a dish. What was left was a yellow oil, which was boiled several times with petroleum ether. Part of the oil did not dissolve. When the concentrated solution was allowed to stand, crystals settled out as elongated needles. M.p. 108-109°. Yield 0.2 g. The m.p. was raised to 110-111° (Base No. 3) after recrystallization from a 1:1 ether-petroleum ether mixture. Further refining did not raise the melting point any higher. This base was freely soluble in alcohol, acetone, methanol, ether, and benzene, and less so in petroleum ether.

2. Haplophyllum pedicellatum

Extraction of alkaloids. The alkaloids were extracted from 10 kg of the air-dry, pulverized plant in the same way as that used for H. perforatum. The alkaloids were extracted from the alkaline solution with ether and then with chloroform. The ether extract yielded 27 g of bases, and the chloroform extract 4.5 g, as a colored crystalline mass. The total base yield was 31.5 g (0.3% of the plant by weight). The mixture was triturated with a small quantity (20-25 ml) of acetone and then suction-filtered. What was left was a mixture of bases freed from tarry impurities.

Skimmianine. The purified mixture of bases was processed with 500 ml of acetone. The insoluble portion was suction-filtered and washed with acetone (mother liquor "C"). The yield was 5 g. M.p. 175-176°. Its mixed melting point with the skimmianine secured previously exhibited no depression.

Processing the mother liquor "C". Haplophine The acetone was driven off to dryness. The residue (20 g) was recrystallized 3 times from dilute alcohol (1:1.5), and from a mixture of equal parts of acetone and petroleum ether (1:20). This yielded colorless crystals with an m.p. of 140-141°. Haplophine is slightly soluble in water and in petroleum ether, more soluble in ether, alcohol, and acetone (1:15), and freely soluble in chloroform.

0.1008 g substance: 0.2520 g CO_2; 0.0484 g H_2O. 0.1076 g substance: 0.2684 g CO_2; 0.0482 g H_2O. 0.1136 g substance: 6.35 ml N_2 (17.5°, 731.9 mm). 0.1246 g substance: 7.1 ml N_2 (15.5°, 724.9 mm). Found %: C 68.22, 63.07; H 5.37, 5.01; N 6.20, 6.32. $C_{13}H_{11}NO_3$. Calculated %: C 68.12; H 4.8; N 6.11.

SUMMARY

1. Three alkaloids have been extracted from the leaves, buds, and young twigs of Haplophyllum perforatum (M.B.) Kar. et Kir.: skimmianine; a crystalline base with an m.p. of 110-11°; and the new alkaloid haploperine $C_{15}H_{13}NO_4(OCH_3)_2$, with an m.p. of 155-156°. Haploperine hydrochloride, with an m.p. of 129-131° (with decomposition), and hexahydrohaploperine $C_{17}H_{25}NO_6$, with an m.p. of 159-160°, have been synthesized. A substance with the composition of $C_{17}H_{17}NO_5$ and an m.p. of 138-139° has been obtained by reacting haploperine with acids.

2. The action of methyl iodide upon haploperine has yielded the isomeric compound isohaploperine: $C_{14}H_{13}O_4(> CO)(>N-CH_3)(OCH_3)$. Haploperine is apparently a derivative of quinoline.

3. The alkaloids are contained principally in the leaves and seeds. The percentage of alkaloids in the leaves rises until the fruit-bearing stage is reached, while the percentage in the twigs diminishes. As the plant develops the percentage of haploperine diminishes during these periods, whereas that of skimmianine increases.

4. The above-ground part of Haplophyllum pedicellatum Bge. contains 0.3% of alkaloids during the flowering period. Skimmianine and a new alkaloid: haplophine $C_{13}H_{11}NO_3$, m.p. 140-141°, have been isolated from the alkaloid mixture.

5. A mixture of alkaloids totaling 0.1% has been extracted from Haplophyllum dubium Eug. Kor. (during the flowering period), from which a base with an m.p. of 95-96° has been isolated.

6. Haplophyllum bucharicum Litv. contains 0.1% of alkaloids during the flowering period. Skimmianine and a base with an m.p. of 151-152° have been isolated from the total alkaloids.

7. Haplophyllum versicolor, Fisch. et Mey contains 0.01% of alkaloids during the flowering period.

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